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**DR. ELI MOSCHCOWITZ**  
 THIS VOLUME IS DEDICATED  
 ON HIS SIXTY-FIFTH BIRTHDAY  
 BY HIS FRIENDS, ASSOCIATES AND PUPILS

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TO

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*Eli Moschcovitz*



## FOREWORD

This volume is dedicated to Dr. Eli Moscheowitz, physician, scientist, scholar, traveller, epicure, bibliophile, magician, and lover of music and the arts. The contributions published in this anniversary volume in honor of his sixty-fifth birthday have been submitted by the authors as evidences of their esteem and affection. No member of the staff of The Mount Sinai Hospital in this generation has commanded the respect and the devotion of his associates in quite the same degree.

Dr. Moscheowitz's association with The Mount Sinai Hospital began as intern, following graduation from the College of Physicians and Surgeons of Columbia University in 1900. Upon completion of his internship in 1903, he spent the following year in Berlin in the pathological laboratory of his friend and teacher, Professor Ludwig Pick. This training led to his appointment as pathologist at the Beth Israel Hospital, New York, where he acquired the fundamental background which determined his subsequent career in clinical medicine. During this period came his early publications in the field of pathology.

In 1920, he joined the staff of the medical service of The Mount Sinai Hospital, and from that time date a series of original contributions to clinical medicine which reflect an increasing awareness of the fact that many disease processes are a reflection of disturbances of the psycho-biologic unit as a whole. These publications attracted wide attention and were frequently quoted, for they are the contributions of a scholarly physician, skilled in the art as well as the science of medicine.

It is difficult for a friend and colleague to assay the relative worth of the great variety of his talents. To many, his capacity for friendship and his worldly philosophy seem outstanding. To others, the freshness of his outlook upon life and his enjoyment of music and of books are most attractive. Undoubtedly, the combination of these qualities is responsible for the fact that the fertility of his mind and the youthfulness of his spirit continue undiminished, and give increasing promise for the future.

GEORGE BAEHR



ELI MOSCHCOWITZ

ON THE DOORSTEP OF THE HOSPITAL

HOWARD LILIENTHAL, M.D.

Competitive tests for positions on the House Staff of The Mount Sinai Hospital were being held and I was one of the investigators. My part was to read the manuscripts and to form my own opinion of the general character as well as of the medical education of the examinee. (That's a correct English word—Century Dictionary.)

As I recollect it, there were about forty candidates and it was no small job to go over the papers.

Chirography has always interested me and even now a manuscript conveys an impression of character, perhaps psychic in type, which could not be given by a type-written page.

Questions answered by Yes or No do not reveal more than the simple knowledge of a fact and, therefore, fuller methods of expression are more informative.

One of the papers, the handwriting atypical, I was inclined to reject—but for my conscience. However, I had not proceeded far when I was struck by the writer's method of revealing not only information but a technical accuracy and mode of expression which would not have been considered an attribute of a mere student. As I recollect, none of the manuscripts was signed, only the number of the candidate being subscribed. The farther I went in this paper the more was I impressed by its maturity and I even admit that I received specific scientific knowledge. I could not do otherwise than place the writer's number at the top of the list.

At my first meeting with Eli Moschcowitz his youthful appearance might well have matched his handwriting; his manner was humorous and inviting. It was then that I learned he was the brother of my friend, Alexis, a surgeon of well recognized importance.

Dr. Eli did not follow his brother's example but became a pathologist and, finally, a general practitioner of medicine and was appointed to the Attending Staff of the hospital which he served for many years, later becoming an active consultant. His knowledge and skill in the diagnosis of unusual cases and in advising therapeutic measures have placed him high in the ranks of his profession.

DR. ELI MOSCHCOWITZ—HIS CONTRIBUTIONS TO THE SCIENCE  
AND ART OF MEDICINE AND RELATED TOPICS

- Non-parasitic Cysts of the Liver with a Study of Aberrant Bile Ducts.  
Am. J. M. Sc., April, 1906.
- Zur Appendicitis Frage. (Co-author A. V. Moschcowitz.)  
Arch. f. klin. Chir., vol. 82, 1907.
- 500 "Surgical Suggestions." (Co-author Dr. Walter Brickner.)  
Surgery Publishing Co., New York, 1907.
- Eosinophilia and Anaphylaxis.  
N. Y. Med. J., January, 1911.
- Thrombosis of Aorta and Both Iliac Arteries following Streptococcus sepsis.  
Proc. N. Y. Path. Soc., vol. 14, January, 1914.
- Vegetative Endocarditis of the Pulmonary Valve.  
Proc. N. Y. Path. Soc., January, 1914.
- Carcinomatous Invasion of the Nerves.  
Virchows Arch. f. path. Anat. 118: 351, 1914.
- Histopathology of Calcification of Spinatus Tendons as Associated with Subacromial  
Bursitis.  
Am. J. M. Sc., 150: 115, 1915.
- William Withering.  
Med. Pickwick, 1: 72, 1915.
- The Relation of Angiogenesis to Ossification.  
Johns Hopkins Med. Bull., vol. 28, March, 1916.
- The Pathological Diagnosis of Diseases of the Appendix Based on the Study of 1500 Specimens.  
Ann. Surg. p. 697, June 1916.
- Ectopic and Latent Chorionepithelioma.  
Proc. N. Y. Path. Soc., 17: 164, 1917.
- A Critique of Banti's Disease.  
J. A. M. A., 69: 1045, 1917.
- Focal Necrosis of the Adrenal Gland.  
Am. J. M. Sc., 156: 313, 1918.
- Congenital Neuroblastoma of the Nose.  
Proc. N. Y. Path. Soc., 18: 57, 1918.
- John Hall: Shakespeare's Son-in-Law.  
Johns Hopkins Med. Bull., June, 1918.
- Hypertension: Its Significance, Relation to Arteriosclerosis and Nephritis and Etiology.  
Am. J. M. Sc., 158: 668, 1919.
- Clinical and Anatomical Relations in Chronic Nephritis.  
Arch. Int. Med., 26: 259, 1920.
- The Treatment of Hypertension.  
Am. J. M. Sc., 159: 517, 1920.
- Hypertension with Minimal Renal Lesions.  
J. A. M. A., 77: 1075, 1921.
- Xanthoma of the Tongue.  
Proc. N. Y. Path. Soc., 22: 135, 1922.
- The Pathology of Hypertension.  
J. A. M. A., 79: 1922.
- Non-Specific Granulomata of the Intestine.  
Am. J. M. Sc., 166: 48, 1923.
- A Case of Gaucher's Disease.  
Proc. N. Y. Path. Soc., 24: 18, 1924.

Congenital Peripheral Resistance: Its Causative Relation to the Precocious Hypertensive States.

Arch. Int. Med., 33: 566, 1924.

The First Editions of Sir Thomas Browne.

Ann. Med. Hist., 6: 363, 1924.

An Unpublished Letter of Sir Thomas Browne.

Ann. Med. Hist., 6: 287, 1924.

An Acute Pleiochromic Anemia with Hyaline Thrombosis of the Capillaries.

Arch. Int. Med., 36: 89, 1925.

Problems on Renal Pathology.

Am. J. M. Sc., 172: 469, 1926.

Pains of Parietal Origin Stimulating Visceral Disease.

J. A. M. A., 88: 897, 1927.

Hypertension of the Pulmonary Circulation.

Am. J. M. Sc., 174: 1927.

Pseudo-, or Transient Arteriosclerosis.

J. A. M. A., 20: 1526, 1928.

Tobacco Angina Pectoris.

J. A. M. A., 90: 733, 1928.

The Cause of Hypertension of the Greater Circulation.

J. A. M. A., 93: 347, 1929.

The Cause of Arteriosclerosis.

Am. J. M. Sc., 178: 244, 1929.

The Natural History of Glomerulonephritis.

New England J. Med., 202: 320, 1930.

The Nature of Grave's Syndrome.

Arch. Int. Med., 46: 610, 1930.

The Pathogenesis of Brown Induration of the Lung.

Am. Heart J., 6: 171, 1930.

The Relation of Achlorhydria to Pernicious Anemia.

Arch. Int. Med., 48: 171, 1931.

Phlebosclerosis of the Hepatic Veins.

Emanuel Libman Anniversary Volumes, 1932.

Der Intravasculäre Druck als Ursache der Arteriosklerose.

Virchows Arch. f. path. Anat. 283: 282, 1932.

A Biologic Concept of Disease.

J. A. M. A., 99: 714, 1932.

A New Sign of Pericardial Effusion.

J. A. M. A., 100: 1663, 1933.

Hypoproteinemia.

J. A. M. A., 100, 1086, 1933.

A Case of Pseudo or Transient Arteriosclerosis.

J. Mt. Sinai Hosp., 1: 11, 1934.

A Psychoanalytic Interpretation of the Constitution in Graves' Syndrome. (Co-author

Sandor Lorand) J. Nerv. & Ment. Dis., 79: 136, 1934.

Psychogenic Origin of Organic Disease.

New England J. Med., 212: 603, 1935.

Allergy to Life: An Interpretation of the Neurotic Constitution.

New England J. Med., 213: 617, 1935.

Arteriosclerosis.

Cyclopedia of Medicine (Piersol), 211, 1935.

Primary Amyloidosis.

J. Mt. Sinai Hosp., 2: 14, 1935.

The Clinical Aspects of Amyloidosis.

Ann. Clin. Med., 10: 73, 1936.

Hiatus Hernia.

J. Mt. Sinai Hosp., 2: 263, 1936.

Bursitis of the Sartorius Bursa.

J. A. M. A., 109: 1362, 1937.

Superior Sulcus Tumor.

J. Mt. Sinai Hosp., 3: 198, 1937.

The Simultaneous Association of Hiatus Hernia and Coronary Disease.

J. Mt. Sinai Hosp., 4: 272, 1937.

Anorexia Nervosa.

Festschrift dedicated to Dr. Robert T. Frank, June, 1937.

The Latent or Albuminuric Phase of Glomerulonephritis.

J. Mt. Sinai Hosp., 4: 993, 1938.

The Nosological Status of Periarteritis Nodosa.

J. Mt. Sinai Hosp., 5: 337, 1938.

The Hemato-Encephalic Barrier. (Co-author Drs. Kessler and Savitsky).

J. Nerv. & Ment. Dis., 90: 594, 1939.

Terminal Ileitis.

J. Mt. Sinai Hosp., 7: 77, 1940.

On Etiology.

J. Mt. Sinai Hosp., 7: 471, 1941.

Causes of Painless Gastro-Duodenal Hemorrhage.

Am. J. M. Sc., 202: 52, 1941.

Effect of Edema and Integumentary Infiltrations on Basal Metabolism Electrocardiogram and Blood Cholesterol.

Arch. Int. Med., 67: 828, 1941.

The Validity of Nephrosis as a Nosological Concept.

J. Mt. Sinai Hosp., 8: 878, 1942.

Potential or Latent Congestive Failure in the Aged.

J. Mt. Sinai Hosp., 9: 663, 1942.

Vascular Sclerosis.

Oxford Press, New York, 1942.

The Hyperkinetic Diseases.

Am. J. M. Sc., 206: 576, 1943.

The Relation of Neurocirculatory Asthenia to Graves' Disease.

Am. Heart J., 28: 177, 1944.

The Electrocardiogram in Uncomplicated Disease of the Gall Bladder and the Changes Induced by Operation.

J. Mt. Sinai Hosp., 10: 632, 1944.

The Biology of Hypertension of the Pulmonary Circulation.

J. Mt. Sinai Hosp., 10: 475, 1944.

The Biology of Hypertension of the Greater Circulation.

J. Mt. Sinai Hosp., 10: 747, 1944.

The Biology of Achlorhydria in Relation to Anemia.

J. Mt. Sinai Hosp., 10: 796, 1944.

The Biological Evolution of Toxic Hepatitis.

J. Mt. Sinai Hosp., 11: 29, 1944.

The Biology of Glomerulonephritis.

J. Mt. Sinai Hosp., 11: 83, 1944.

The Biology of Polycythemia Vera.

J. Mt. Sinai Hosp., 11: 232, 1944.

The Biology of Follicular Lymphoblastoma.

J. Mt. Sinai Hosp., 11: 298, 1945.

The Biology of Obesity.

J. Mt. Sinai Hosp., 11: 357, 1945.



## STIGMATA OF INFERTILITY

ROBERT T. FRANK, M.D.

The gynecologist and endocrinologist are consulted by childless couples who seek help. Previous investigation has demonstrated that the husband's semen is normal, his genito-urinary tract is uninfected and that he is virile.

The wife, likewise, has been shown to have a permeable uterus and tubes, her cervix is uninflamed, her menstruation regular. Study of vaginal smears, endometrial biopsy, excretion of pregnandiol, have given as conclusive evidence as our present methods permit, that her cycles are ovulatory. Her basal metabolism is normal. Semen insufflation has been tried and yet no pregnancy occurs.

These are trying and puzzling problems. The well informed specialist searches, and too often searches in vain for some explanation. He knows and recognizes well known constitutional stigmata such as eunuchoid and infantile build, marked obesity, hirsuties, a persistently infantile uterus, etc., which occur with frequency in the sterile group, but he is aware that the significance of these findings is not absolute, that accentuation of familial traits may minimize their importance.

I desire to call attention to several stigmata, which, during the course of many years, I have noted in the sterile group under discussion. Again it should be emphasized that these are not absolute criteria of sterility, rather they are constitutional marks of the low fertility group.

The Levi-Lorraine type of infantilism is well known and recognized. There are some women, however, who do not fall into this group, but are contiguous to it. By anthropometric evaluation they prove normal. However, their appearance of over-youthfulness, their mincing voice, their small-pored delicate skin, their fine silky hair, their thin bones and weak musculature, their small hands and feet unmask them to the trained observer. As a group these women fall into the least fertile class.

Minor deviations in the breast development are of frequent occurrence and of little significance. They include large, small, asymmetrical, accessory breasts, retracted nipples, etc. There is one breast change, however, to which I ascribe importance, particularly as it may be detected immediately after puberty. In default of a better name, I call it the "cup shaped areola." Usually these areolae are large. Instead of being flat, as is normal, the entire areola bulges upward above the breast and on its summit is the nipple. It gives the impression of a weakening of the fascial sheath which envelops the breast, with consequent symmetrical extrusion of the breast tissue at the site of the ring. In my experience this sign appears with significant frequency in the infertile group (figs. 1 and 2).

In performing pelvic examinations, I have noted a sinistro-position of the uterus in a number of nulliparous patients, including virgins. No history of antecedent inflammation can be elicited. Nor is there any sign of inflammation



FIG. 1. "Cup shaped areola." A. Adolescent breast. B. Adult breast



FIG. 2. Schematic antero-posterior section of breast. 1. Normal. 2. "Cup shaped areola"

present. By vaginal or rectal examination, both cervix and fundus are situated close to the left pelvic wall. The fundus, usually is in ante flexion, sometimes retroflexed. The left parametrium is short but not infiltrated, the right correspondingly elongated and thin. The left adnexae are high, close to the pelvic wall and above the fundus, the right adnexae are in a normal position and there-

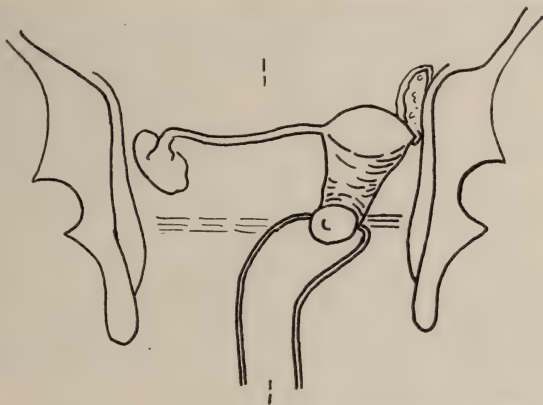


FIG. 3. Schematic transverse section of pelvis showing congenital sinistroposition of uterus. Note consequent elongation of right cardinal ligament

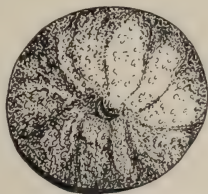


FIG. 4. Congenital cervical erosion. Normal nulliparous external os. Uniform involvement of entire portio vaginalis

fore elongated. These findings are permanent and uninfluenced by the fullness or emptiness of the sigmoid flexure (fig. 3).

The condition has been noted in early adolescence and persists. It appears to be congenital. I have not had the opportunity of viewing it when the abdomen is opened. However, I feel certain that the uterus is symmetrical and the adnexae are equally developed on both sides. If this were not the case,

one might be tempted to ascribe the condition to partial aplasia of one Müllerian duct with a minor degree of uterus unicornis. Under the circumstances, I am unable to offer any explanation of the causation. The frequency of sterility in these patients has become apparent to me and I consider it of major prognostic significance.

Finally, I desire to call attention to a condition of the cervix which, too often, is diagnosed incorrectly. It is the congenital erosion, a non-inflammatory lesion (fig. 4). Instead of a smooth, pale normal portio, the entire area is velvety, deep red and vascular. However, the absence of an infected mucopurulent cervical plug is striking. Characteristic is the uniform involvement of the entire portio. Biopsy shows a surface consisting of shallow, closely approximated folds covered by a single layer of high cylindrical (cervical) epithelium with basal nucleus. The condition does not respond to astringent applications or to cauterization. In one patient whom I had the opportunity of observing for many years and in whom X-ray castration was induced for other reasons, this erosion was uninfluenced by induction of the artificial menopause.

The congenital erosion, as its name implies, dates from the early fetal stage. Normally, the cylindrical epithelium (Müllerian derivation), which covers the portio, is replaced by the multilayered squamous epithelium (urogenital sinus derivation) which clothes the vagina when Müllerian duct and sinus coalesce at the third month of fetal life. In these patients the fetal state persists indefinitely. *Per se* the erosion is of no significance. However, it appears most often in patients who have never been able to conceive.

The stigmata, to which I have called attention, should be taken into account in evaluating the fertility or infertility of a patient, in the same way that the profession generally considers an infantile uterus (long, narrow, with cervix-fundus ratio 1:1 instead of 1:4) of significance. This will counterbalance the purely mechanistic viewpoint (permeability of cervix and tubes) as well as the exaggerated "endocrine" concept of anovulatory cycle or the still vaguer diagnosis of "ovariopituitary dysfunction" which so often is used to hide our ignorance. Some patients are so constituted that they conceive readily. Others—fortunately for the race, few in number—conceive with difficulty and then only at rare intervals. Others never become pregnant. At best, the size up of these patients, even after all available data have been evaluated, is not conclusive and therefore the prognosis given never should be dogmatic or hopeless.

## CONGENITAL ATRESIA OF THE ESOPHAGUS WITH TRACHEOESOPHAGEAL FISTULA<sup>1</sup>

ERNEST E. ARNHEIM, M.D.

Congenital atresia of the esophagus with or without a fistula communicating with the trachea comprises a difficult problem in pediatric surgery. Surgeons of the past had found the problem insoluble and it is only within the past five years that a successful solution has been found, but it is still the feeling of many surgeons and pediatricians alike that this condition is incompatible with life and that it is useless to attempt operation.

Although atresia of the esophagus with or without tracheoesophageal fistula is not a common condition, about 450 cases have been reported in the literature. The outstanding communications have been those of Plass (17), Vogt (23), Rosenthal (19), O'Hare (16), Ashley (1), Leven (12, 13), Shaw (21), Lanman (11), Haight and Towsley (7), Ladd (9), Humphreys (8), and Haight (4). Plass and Rosenthal have considered the embryologic aspects in detail.

There is a variety of classifications of congenital anomalies of the esophagus, but for simplicity and usefulness I employ the one used at the Children's Hospital, Boston, described by Ladd and originally suggested by Vogt. These anomalies are divided into four types. In type I, the upper blind pouch of the esophagus ends at about the level of the first or second dorsal vertebra, and the lower end of the esophagus begins again as a blind pouch at the level of the fourth or fifth dorsal vertebra. In type II, the upper pouch of the esophagus ends in a fistulous tract entering the trachea just above its bifurcation, the lower segment being blind. In type III, the upper segment ends blindly, and the lower segment of the esophagus communicates with the trachea just above its bifurcation; this is by far the most common type. The communication with the trachea may be at the carina instead of above the bifurcation. In type IV, both the upper and lower segments communicate with the trachea. These types can be accurately diagnosed before operation, and the knowledge of these variations has clinical application in the surgical management of these anomalies.

### CLINICAL FEATURES

The symptoms of congenital atresia of the esophagus are noted soon after birth. The infant is seen to have an excess of saliva in the mouth with a resulting choking and, usually, some cyanosis. When a feeding is given there is immediate regurgitation with aspiration of the fluid into the air passages and an increase in the choking and cyanosis. Examination of the chest often reveals moist rales in the lungs, usually in the right upper lobe. The findings on abdominal examination vary depending upon whether there is or is not a fistulous communication of the lower pouch of the esophagus with the trachea. In type I and II, previously described, air cannot enter the intestinal tract and the ab-

<sup>1</sup> From the Pediatric Services of Dr. Bela Schick and Dr. Murray H. Bass and the Surgical Service of Dr. Harold Neuhof, The Mount Sinai Hospital, New York, N. Y.

domen is scaphoid. In types III and IV, air enters the stomach through the fistulous communication of the lower pouch of the esophagus with the trachea and the abdomen is more or less distended.

Roentgenologic examination is of great aid in diagnosis. In this connection the use of a contrast medium, particularly barium, is not advisable. If any such medium is used, lipiodol is more safe, but any information gained by its use can be more safely and easily obtained without its use. Aspiration into the air passages on a contrast medium adds to the dangers of pneumonia, already usually present. The technic of roentgenologic examination is as follows: A soft rubber catheter, usually about size 12F., is passed down the esophagus as far as it will go. If it meets an obstruction about 10 to 12 cm. from the mouth, the diagnosis of congenital atresia of the esophagus is confirmed. A roentgenogram with the catheter in place will then demonstrate the site of obstruction. The roentgen examination should include the abdomen to differentiate the type of malformation. In types I and II, there is no air in the stomach or intestinal tract; in types III and IV, there is air in these viscera.

Congenital anomalies of the esophagus are frequently associated with anomalies of other organs of the body, and some of these abnormalities in themselves may be incompatible with life unless corrected surgically. In the recent report by Ladd of the experiences of the Children's Hospital, Boston (9), there were 63 congenital anomalies in 72 cases of congenital atresia of the esophagus; the most frequent being anomalies of the heart and aorta and urinary tract, Meckel's diverticulum, and imperforate anus.

#### TREATMENT

There are two plans of surgical treatment of congenital atresia of the esophagus, which, for purposes of simplicity, may be termed the indirect and the direct procedures. The former utilizes the principle of staged operations, and has been used by Richter (1913) (18), Scott (1928) (20), Mixter (1929) (15), Leven (1936 and 1941) (12, 13), Gage and Ochsner (1936) (3), Carter (1941) (2), and Ladd (1944) (9). These indirect procedures have been variously modified, but, in general, follow the following principles: (1) extrapleural ligation of the tracheoesophageal fistula; (2) exteriorization of the upper esophageal pouch; (3) gastrostomy; (4) construction of an anterior thoracic esophagus.

The direct plan consists of an extrapleural ligation of the tracheoesophageal fistula and restoration of the continuity of the esophagus by an anastomosis of the proximal and distal ends. This procedure has been performed by Shaw (1939) (21), Lanman (1940) (11), Haight and Towsley (1943) (7), Humphreys (1944) (8), Ladd (1944) (9), and Haight (1944) (4).

The main disadvantage of the indirect plan is that it involves a number of surgical procedures, the most difficult of which is the construction of an anterior thoracic esophagus by a skin-lined tube. It is, however, the procedure of necessity when the distance between the esophageal segments is too great to allow a primary anastomosis. The direct anastomosis is the operation of choice, but it presents many technical difficulties due to the small size of the distal segment of



the esophagus, the distance between the two ends, and the structure of the esophageal wall. That these difficulties, however, can be overcome, is shown by the experience of Haight (4), who was able to perform an anastomosis in 16, or 66.7 per cent, of 24 patients for whom an exploration was performed. A supplementary gastrostomy is often necessary because of leakage from the anastomosis. The details of the operative procedures are fully described in the publications of Leven (12, 13), Carter (2), Lanman (11), Humphreys (8), Ladd (9), and Haight (4), and in the case reports to follow in this communication.

The problem of pneumonia is a serious one, for it is the chief cause of death, and, in many instances, is present before operation. It is hoped that with the advent of penicillin this serious complication can be successfully treated. Haight (5) states that "in subsequent cases admitted with extensive pneumonia, the plan would be to give penicillin and hope that the pneumonia could be overcome in a period of several days, and then proceed with operation."

It is only within recent years that these operative procedures have been successfully performed. The largest number of operative recoveries have been reported by Ladd (9) and Haight (4). In a series of 34 cases of atresia of the esophagus operated upon by Ladd and Gross from 1940 to 1944, 6 patients had direct anastomoses with 2 recoveries, and 28 patients had the staged procedures with 9 recoveries. The oldest of these patients is  $4\frac{3}{4}$  years of age, and 8 patients are under 1 year of age. In 2 of the 9 recoveries with staged procedures the anterior thoracic esophagus had been completed. In a subsequent report Ladd (10) stated that 13 patients were operated upon in 1944, of whom 8 are living. In 5 of these patients a primary anastomosis was performed, and 2 are living. In the other 8 patients the fistula was tied off, and esophagostomy and gastrostomy performed, and 6 are living. Haight and Towsley (7) reported the first successful case of anastomosis for congenital atresia of the esophagus with tracheoesophageal fistula in 1943, the operation having been performed in 1941. Haight (4) has had the greatest experience with primary anastomosis, and was able to perform anastomoses in 16, or 66.7 per cent, of 24 patients explored. Six, or 37.5 per cent, of the 16 patients for whom an anastomosis was done are living from 7 months to  $3\frac{1}{2}$  years after operation. The reconstructed esophagus was patent in all instances. In a recent communication Haight (6) stated that he had performed 5 additional anastomoses with 1 survival. Leven (13) reported 1 patient who was living 1 year after the first operation by the staged indirect method, but the anterior thoracic esophagus had not been constructed. In a subsequent communication Leven (14) stated that the child was  $4\frac{1}{2}$  years of age, and that he has had 4 additional survivals by the staged indirect method awaiting construction of the anterior thoracic esophagus. Humphreys (8) reported 3 survivals in 6 patients operated upon by the indirect procedures, but in these the anterior thoracic esophagus had still to be constructed. The same author reported 1 successful direct anastomosis of the esophagus 122 days after birth, in a group of 6 patients operated upon by this method. In a recent communication Shaw (22) stated that a patient, operated upon by direct anastomosis, was alive and well 11 months after operation.



Prior to these successful results, other surgeons had been successful in performing direct anastomosis of the esophagus, but unfortunate circumstances contributed to the death of the patients. Lanman (11) was the first to utilize the procedure of direct anastomosis of the esophagus and closure of the tracheoesophageal fistula, and reported 4 patients operated upon by this technic in 1936 and 1937. In one of these patients who lived 9 days, death was due to overhydration with intravenous fluids. The first reported immediately successful direct anastomosis was described by Shaw (21) in 1939, and death was attributed to a transfusion reaction on the twelfth postoperative day.

In this discussion of operative treatment the importance of adequate pre- and postoperative management by well-trained pediatric and nursing staffs is stressed. Mucus should be aspirated from the pharynx and oxygen therapy instituted. The care of pulmonary complications by sulfonamides or penicillin is essential. As a preoperative measure, which should be continued during and after operation, the administration of parenteral fluids is of great importance. This is supplemented by transfusions of whole blood or plasma as indicated. Ascorbic acid and vitamin K are routinely administered before operation.

#### CASE REPORTS

*Case 1. History* (Adm. 497752): J. J., a male infant, aged 77 hours, was admitted to the Mount Sinai Hospital on November 10, 1942. The infant was a first child, born at term with the aid of forceps. A left facial paresis was noted at birth, but no other abnormalities were found at this time. The birth weight was 5 pounds and 7 ounces. During the second day of life an absence of the anus was noted, but there were no evidences of intestinal obstruction. A small amount of water had been given by mouth during the second day, followed by vomiting. The perineum was explored at another hospital on the third day of life, but the rectum was not found. Slight cyanosis was noted after operation. A hypodermoclysis of 150 cc. of glucose had been administered.

*Examination:* The temperature was 97°F., and the weight 5 pounds and 5 ounces. The infant, although small, was normally developed. The abnormal findings were a left facial paresis, cyanosis, icterus, and an imperforate anus with a fresh operative wound in the perineum. The abdomen was not distended.

*Laboratory Data:* Urine: no abnormalities. Blood: hemoglobin, 112 per cent; red cells, 6,270,000; leucocytes, 12,150, of which there were 19 per cent segmented polymorphonuclear leucocytes, 44 per cent nonsegmented polymorphonuclear leucocytes, 21 per cent lymphocytes, 14 per cent monocytes, and 1 per cent myelocytes.

A roentgenogram of the abdomen (without the use of a contrast medium) (fig. 1), taken on the day of admission, revealed an absence of gas in the intestinal tract; a catheter was passed into the esophagus which was obstructed at the level of the seventh cervical vertebra. The lungs showed roentgen evidence of a consolidation of the upper third of the right lung.

The infant was observed for a period of twelve hours during which time he had frequent episodes of cyanosis and vomiting of mucus which were relieved by catheter suction through the pharynx. The child was placed in an oxygen cubicle, and a hypodermoclysis of 40 cc. of normal saline was administered. A continuous intravenous infusion of 5 per cent dextrose in physiologic solution of sodium chloride was started, and operation was performed.

*Operation:* Through a 5 cm. left upper rectus incision (under local anesthesia), the stomach was exposed and appeared to be of normal size. A Witzel gastrostomy, using a no. 12 F. open-end catheter, was performed.

*Course:* The infant withstood the operative procedure well. Oxygen therapy in a cubicle, pharyngeal suction, and intravenous fluids were continued. Episodes of cyanosis were

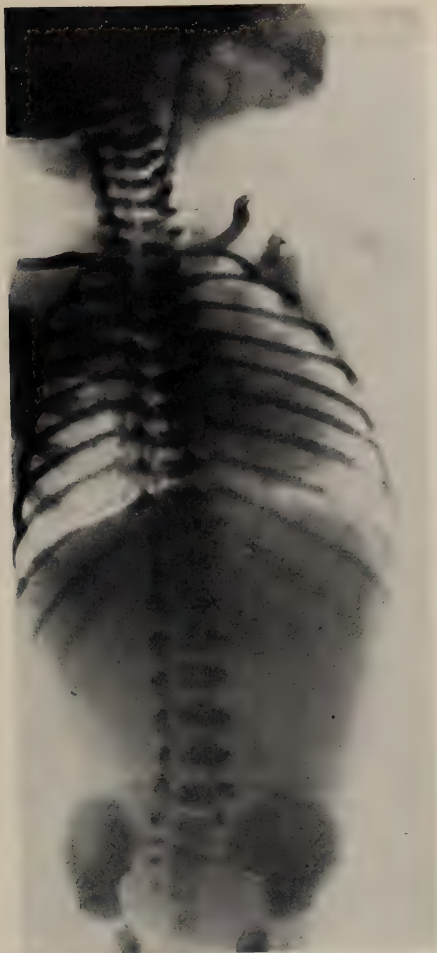


FIG. 1. Roentgenogram of the chest and abdomen (without the use of contrast medium) on admission showing an absence of air in the gastrointestinal tract, a catheter in the esophagus obstructed at the level of the seventh cervical vertebra, and a consolidation of the upper third of the right lung.

relieved by suction. A transfusion of 70 cc. of citrated blood was administered during the first postoperative day. The temperature remained normal, but the respiratory rate was between 60 and 75 per minute. Feeding by gastrostomy was started on the second postoperative day.

*Operation:* A sigmoid colostomy was performed two days after the gastrostomy, on the fifth day of life. Under local anesthesia a 3 cm. left rectus incision was made. Bile-stained fluid was found in the peritoneal cavity. The small intestines were completely collapsed, measuring about 3 mm. in diameter. The sigmoid colon contained air and was bluish in color; it measured about 1.5 cm. in diameter. The wall of the sigmoid was sutured to the parietal peritoneum, leaving an area of colonic wall exposed. Small packings were inserted around the bowel.

*Course:* The same therapeutic measures outlined in the previous postoperative course were continued. On the third day after the colostomy, it was noted that the gastrostomy feedings of evaporated milk and water took a prolonged time to run in by gravity. The temperature remained normal, but the respiratory rate continued to be rapid. Examination of the chest revealed coarse rhonchi over the right anterior lung field. The colostomy was opened on the third day after exteriorization of the sigmoid, and thick, sticky meconium was evacuated. Roentgen examination of the chest on the fifth day of hospitalization revealed a consolidation involving the upper portion of the right lung and, to a lesser extent, the lower half of the right lung. Sodium sulfadiazine was administered parenterally on the sixth hospital day. The gastrostomy feedings continued to require long periods to gravitate through the tube. Additional fluids were administered daily by hypodermoclyses. The condition of the infant remained poor and he died on the eighth hospital day.

*Necropsy Findings:* The body was that of an 11 day old, well developed and fairly well nourished male infant. There was a moderate amount of yellowish fluid in the peritoneal cavity. Fibrinous exudate was present around the stomach, on the anterior surfaces of the spleen and liver, and in the lesser sac. There were fibrinous adhesions around the stomach, duodenum, and gall bladder. The area around the colostomy wound was clean.

The proximal portion of the esophagus was moderately dilated and ended blindly about 2 cm. above the bifurcation of the trachea. There was a thin, fibrous cord, without a lumen, extending from this point, along the posterior surface of the pericardial sac, to the cardia of the stomach. The distal end of the esophagus was represented by a blind sac, 0.5 cm. long. It was located under the diaphragm, and opened into the stomach at the cardia. The stomach was markedly dilated, its wall moderately thickened, and it contained a large amount of reddish brown fluid. The gastrostomy tube was in situ. The pyloric ring was markedly dilated. The proximal portion of the duodenum was also distended, measuring about 3 cm. in diameter, and ended blindly (atresia) at the junction of its first and second parts. The second part of the duodenum was of normal width and thickness, the common duct opening into it at the papilla of Vater. The remainder of the small intestine was normal, containing green meconium. The colon presented no abnormalities except for the sigmoid colostomy. The rectum was moderately dilated and ended as a blind pouch 3 cm. above the cutaneous surface of the perineum.

The other abnormal findings were hypertrophy of the right kidney; hypoplasia and cystic degeneration of the left kidney; atresia of the left ureter; bronchopneumonia of both lower lobes.

*Comment:* This infant presented the most unusual combination of three atresias of the esophagointestinal tract, involving the esophagus, duodenum, and rectum. The only atresia obvious at birth was that of the rectum. An atresia of the esophagus was suspected because there were no clinical evidences of intestinal obstruction, present after the first day of life in infants with atresia of the rectum. In fact, there was no air visible in the gastrointestinal tract by roentgen examination. The atresia of the esophagus prevented the air from entering the

stomach and intestines. The frequent episodes of cyanosis and vomiting of mucus were also indicative of an atresia of the esophagus. The roentgen examination indicated that the anomaly of the esophagus was of types I or II, described above. The necropsy findings revealed the unusual nature of this anomaly—the atresia extending to the diaphragm. It was safe to perform a gastrostomy, since there was no clinical evidence of a tracheoesophageal fistula. Once this was performed, it was necessary to proceed with a colostomy to obviate an intestinal obstruction. The atresia of the duodenum was not diagnosed, although it had been noted that the gastrostomy feedings took a prolonged period of time to run in by gravity after the fifth day following gastrostomy. The atresia of the duodenum was also unusual, in that it was located above the ampulla of Vater. There were also anomalies of the urinary tract, and the usual bronchopneumonia.

*Case 2. History* (Adm. 502177): I. K., a male infant, aged 2 days was admitted to the Mount Sinai Hospital on February 27, 1943. The infant was a first child, born prematurely after  $7\frac{1}{2}$  months of pregnancy. The birth weight was 4 pounds and 12 ounces. He had regurgitated all feedings since birth, and had passed a small amount of meconium by rectum. A large amount of mucus was noted in the pharynx. A few hours before admission the chest was examined by fluoroscopy and a small amount of barium mixture was given by mouth, which appeared to meet an obstruction at about the level of the second dorsal vertebra.

*Examination:* The temperature was  $97^{\circ}\text{F}$ ., and the weight 4 pounds and 10 ounces. The infant, although small, was normally developed. The abnormal findings were icterus, coarse rhonchi throughout both lungs and slight dullness to percussion over the right upper lobe of the lung anteriorly.

*Laboratory Data:* Urine: no abnormalities except for a few white and red blood cells on microscopic examination. Blood: hemoglobin, 110 per cent; hematocrit, 46 per cent; proteins, 7.18 per cent.

A roentgenogram of the abdomen (without the use of a contrast medium) (fig. 2, taken on the day of admission, revealed a moderate amount of air in the stomach and intestines; a small amount of opaque material was in the stomach (barium administered prior to admission). A catheter was passed into the esophagus, meeting an obstruction at the level of the superior thoracic aperture; the esophagus up to this point appeared to be displaced to the left. The lungs revealed roentgen evidence of a consolidation of the right upper lobe and a few areas of greater density, probably representing barium.

The infant was observed for a period of sixteen hours during which time he was placed in an oxygen cubicle, and a hypodermoclysis of 180 cc. of normal saline, and sodium sulfadiazine parenterally, were administered.

*Operation:* Through a 5 cm. left upper oblique muscle-splitting incision (under local anesthesia), the stomach was exposed and appeared to be of small size. A Witzel gastrostomy, using a no. 12 F. open-end catheter, was performed.

*Course:* The infant withstood the operative procedure well. The therapeutic measures outlined in the preoperative course were continued with the addition of 40 cc. of plasma intravenously six hours after operation. During the first postoperative day feedings through the gastrostomy tube resulted in regurgitation of fluid through the nose and mouth. The temperature rose to  $104^{\circ}\text{F}$ ., but dropped to  $101.4^{\circ}\text{F}$ . on the same day. Associated with the rise in temperature, the respirations were very rapid and rales were heard in both lungs.

*Operation:* The second operation was performed on the day after the gastrostomy. Under cyclopropane anesthesia, an incision was started at about the level of the first and second ribs to the right of the spine and continued downward and parallel to the spine to about the level of the fifth rib, where it was curved laterally below the scapula and continued to the axilla. The fifth (?) rib was resected subperiosteally for a distance of about 4 cm., starting close to the transverse process. In order to obtain more adequate exposure, a

section of the same amount of the sixth (?) rib was removed. The intervening intercostal muscle was excised from the underlying pleura, starting close to the spine. The pleura was dissected laterally so as to expose the posterior mediastinum. The azygos vein was



FIG. 2. Roentgenogram of the chest and abdomen (without the use of a contrast medium) on admission showing air in the gastrointestinal tract, and catheter in the esophagus obstructed at the superior thoracic aperture, and a consolidation of the right upper lobe in which a small amount of barium is visible.

exposed crossing the operative field horizontally. Exploration of the posterior mediastinum revealed, what appeared to be, the lower segment of the esophagus, lying behind the azygos vein. This structure was about 5 mm. in diameter. Two no. 5 silk sutures were



passed around it and tied. The defect in the thoracic wall was partially closed with two pericostal silk sutures. The musculature of the thoracic wall and the skin were closed with interrupted silk sutures. An intravenous infusion of 40 cc. of plasma was administered.

*Course:* The infant withstood the operative procedure well. Upon returning to the ward the infant was dyspneic, and about four hours after operation marked edema of the eyelids was noted. The respirations became irregular and more infrequent, and the edema more generalized. The infant died fifteen hours after operation, at the age of 6 days.

*Necropsy Findings:* The pleural cavities contained a moderate amount of yellow fluid. The parietal pleura showed a few hemorrhages near the mediastinum. The posterior mediastinum was clean. A ligature was found about the aorta just below the arch. The esophagus was funnel-shaped being wide at its upper end and continuing into a cord-like stricture at the level of the thyroid; the esophagus could not be probed below this level. The lower end of the esophagus communicated with the trachea through a fistulous communication about 8 mm. above the bifurcation of the trachea.

The other abnormal findings were bilateral pneumonia and focal areas of atelectasis; patent foramen ovale; patent ductus arteriosus; congestion of abdominal viscera; generalized edema.

*Comment:* The history and examination of this premature infant were typical of congenital atresia of the esophagus, and the roentgen examination indicated a type III anomaly. The dextraposition of the descending thoracic aorta led to the error of mistaking this structure for the esophagus; pulsations were not noted, probably due to the low blood pressure and rapid cardiac rate. Anatomically, the aorta lay in the position of the esophagus beneath the azygos vein on the right side, and the error illustrates the difficulty in identifying anatomical structures in a limited operative field in a premature infant. With the more complete exposure of the mediastinum employed in later cases, this error would probably not be made. It is of interest that the infant lived for a period of fifteen hours after operation. Dextraposition of the aorta was present in one of the cases reported by Lanman (11), in which the operation consisted in exploration of the mediastinum by the transpleural route, but the infant died just as the mediastinum was entered. In this case a patent ductus arteriosus was also present.

*Case 3. History* (Adm. 519456): J. S., a male infant, aged 6 days, was admitted to the Mount Sinai Hospital on April 26, 1944. The birth weight was 6 pounds. The infant had vomited all feedings since birth. During the first four days of life he required oxygen therapy. On the fifth day of life, in another hospital, barium was passed into the esophagus by catheter, visualizing a blind upper pouch; some barium passed into the lungs and the stomach; air was present in the stomach and intestines (fig. 3).

*Examination:* The temperature was 98°F., and the weight was 6 pounds. The infant was dehydrated and coughing large amounts of mucus. Cyanosis was marked and the respiratory rate was about 100 per minute. There was considerable difficulty with breathing and retraction of the thoracic wall on inspiration. Examination of the chest revealed numerous rales throughout both lungs. Other abnormal findings were an absence of the left thumb, and an Erb's palsy of the left upper extremity.

*Laboratory Data:* Urine: no abnormalities except for some white blood cells and casts on microscopic examination. Blood: hemoglobin, 116 per cent; leucocytes, 16,300, of which there 51 per cent segmented polymorphonuclear leucocytes and 14 per cent non-segmented, 26 per cent lymphocytes, 5 per cent monocytes, 1 per cent eosinophiles, and 3 per cent myelocytes.

A roentgenogram of the chest revealed scattered areas of consolidation throughout both lungs.



FIG. 3. Roentgenogram of the chest and abdomen (barium administered) 1 day before admission showing a dilated upper pouch of esophagus, barium deposits in the lungs, and air in the intestines.

The infant was observed for a period of twenty-four hours during which time he was kept in an oxygen cubicle, and 250 cc. of a mixture of 5 per cent dextrose in distilled water and physiologic solution of sodium chloride were administered through a continuous intravenous



drip; 60 cc. of plasma, and sulfadiazine, were also given intravenously. There was no improvement in the condition of the infant during this period.

*Operation:* Operation was started under local anesthesia with the infant in the left lateral decubitus position. A curvilinear periscapular incision was made on the right side extending from the base of the neck around the vertebral border of the scapula to the axilla. The scapula and its attached muscles were reflected upward from the thoracic wall. The third and fourth ribs were resected subperiosteally from their spinal attachments to the axilla. The intercostal vessels between the ribs were divided and ligated and the intercostal musculature removed. This allowed exposure of a segment of parietal pleura, measuring about 6 by 3 cm. in diameter.

The parietal pleura was stripped down by blunt dissection off the vertebral bodies until the posterior mediastinum was exposed, and the dissection was continued until the esophagus and the trachea were exposed. The right vagus nerve was clearly visualized. The communicating branch of the azygos vein was clamped, divided and ligated. The lower segment of the esophagus was clearly visualized and found to be quite adherent to the trachea; it was quite narrow, measuring about 4 mm. in diameter. It entered the trachea through a small communication which was clamped, divided, and ligated with 4-0 silk. The upper segment of the esophagus was exposed and found to end blindly about 1.5 cm. proximal to the distal end. Visualization of the upper segment was difficult because of its height, and assistance was rendered by pressure on the catheter which had been inserted prior to operation. The proximal segment of the esophagus was approximately 1 cm. in diameter. The blind end was opened. The catheter was passed through it into the open end of the distal segment of the esophagus and down into the stomach. Tension sutures of 5-0 silk had been passed into the four quadrants of the esophageal wall prior to the opening of the proximal end of the esophagus. An end-to-end anastomosis of the esophagus was carried out by interrupted opposing sutures of 5-0 silk through the open ends of the esophagus. These were reinforced by a few mattress sutures of the same material, and then by tying of the stay sutures which had been inserted first; the latter were tied under slight tension. About 0.5 gm. of sulfanilamide powder was scattered in the posterior mediastinum. The thoracic wall was closed with interrupted sutures of 4-0 silk. The operation was considerably prolonged by the frequent rapid expansion and deflation of the lung.

*Course:* The infant withstood the operative procedure well. Oxygen therapy in a cubicle, pharyngeal suction, sulfadiazine, and intravenous fluids were continued. In addition, an infusion of 60 cc. of citrated blood was administered during the first postoperative day. The postoperative course during the first twenty-four hours was very satisfactory. The respiratory rate remained rapid, but there was no cyanosis nor dyspnea. Examination of the lungs revealed rhonchi on both sides. Feedings of 5 per cent dextrose in distilled water through the catheter passing through the anastomosis were started on the second postoperative day. A mixture of sulfadiazine in water was made up and administered through the catheter. On the fifth administration of the sulfadiazine, it was noted that the catheter was obstructed and did not allow passage of fluid through it. The lack of available veins for intravenous therapy and the inadequacy of hypodermoclyses for sufficient nutrition made gastrostomy imperative.

*Operation:* Through a 6 cm. left upper rectus incision (under local anesthesia), the stomach was exposed and found to be of normal size. A Witzel gastrostomy, using a no. 12 catheter, was performed. The infant's condition during operation was poor; he appeared pale and cyanotic and had irregular rapid respirations.

*Course:* The infant's condition remained poor, and he died one hour after the gastrostomy, at the age of 9 days.

*Necropsy Findings:* The right pleural cavity contained a small amount of fluid. The operative incision was made through the chest wall outside of the pleura; the third and fourth ribs had been partially removed. The wound appeared clean, and the parietal pleura and the mediastinum were focally congested.

The esophagus showed several black silk sutures around its entire circumference, about 1 cm. above the bifurcation of the trachea. The upper portion of the esophagus was widely patent, measuring about 0.7 cm. in diameter. There was an end-to-end anastomosis of the esophagus about 1 cm. above the bifurcation of the trachea (fig. 4). On filling the stomach with water, a small trickle was noted through the antastomosis. The entire esophagus could



FIG. 4. Photograph of the thoracic organs at necropsy showing the site of the end-to-end anastomosis of the esophagus (arrow).

be probed. The trachea showed on its posterior wall, 1 cm. above the bifurcation, a small funnel-shaped orifice ending blindly, about 2 mm. in length; one silk suture was found about 0.5 cm. below it (fig. 5). A narrow tube, stitched to the wall of the stomach, led into the lumen of the stomach near the greater curvature.

The other abnormal findings were bronchopneumonia and atelectasis of both lower lobes of the lungs, congenital absence of the left kidney and ureter; congenital absence of the left thumb; patent ductus arteriosus.

*Comment:* The infant's condition upon admission was very poor and there were evidences of a bilateral pneumonia. Therapeutic measures for a period of twenty-four hours, did not produce any appreciable improvement, and it was questionable whether the infant could survive operation. In spite of this, an

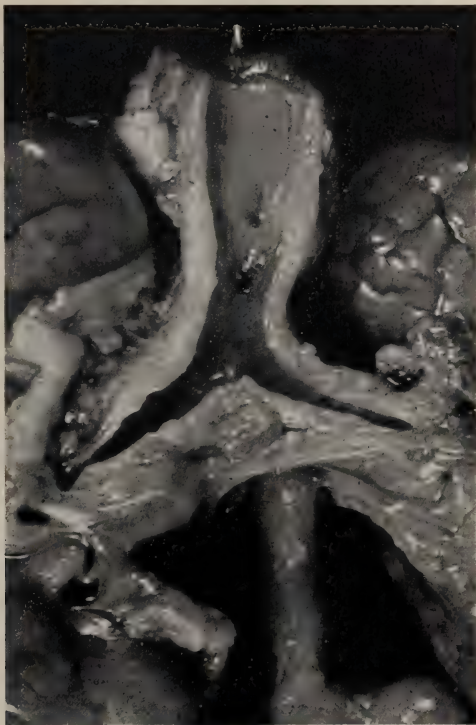


FIG. 5. Photograph of the opened trachea at necropsy showing the site of the closed tracheo-esophageal fistula on the posterior wall.

anastomosis of the esophagus was performed. The unfortunate plugging of the tube with sulfadiazine contributed to the death of the patient, in that feedings through the tube could have been continued for a longer period, and, if a gastrotomy did become necessary, it could have been performed at a later date when the condition of the infant had improved. The other congenital anomalies were not incompatible with life.

*Case 4. History* (Adm. 520728): C. M., a male infant, aged 4 days, was admitted to The Mount Sinai Hospital on May 25, 1944. The infant was a second child, born at term. The birth weight was 5 pounds and 6 ounces. He had regurgitated all feedings since birth. Before admission the infant had been given a barium mixture by mouth which met an obstruction in the upper esophagus.

*Examination:* The temperature was 98.6°F., and the weight 5 pounds and 6 ounces. The infant was normally developed. The abnormal findings were retraction of the thoracic wall on inspiration, and rales at both bases of the lungs.

*Laboratory Data:* Urine: no abnormalities except for albumin. Blood: hemoglobin, 127 per cent; red cells, 6,400,000; leucocytes, 10,000, of which there were 13 per cent segmented polymorphonuclear leucocytes and 28 per cent non-segment, 53 per cent lymphocytes, 2 per cent monocytes, and 4 per cent eosinophiles.

A roentgenogram of the chest (fig. 6) revealed scattered infiltrations throughout the right upper lobe, both pulmonary bases, and the parahilar area; a catheter was passed into the esophagus and was seen to be obstructed in its upper portion; air was present in the gastrointestinal tract.

The infant was observed for a period of twenty-four hours during which time he was kept in an oxygen cubicle, and 150 cc. of physiologic solution of sodium chloride were administered through a continuous intravenous drip; 50 cc. of plasma, and sulfadiazine were also given.

*Operation:* The operation was started under local anesthesia with the infant in the left lateral decubitus position. A curvilinear periscapular incision was made on the right side, extending from the base of the neck around the vertebral border of the scapula to the axilla. The scapula and its attached muscles were reflected upward from the thoracic wall. The third and fourth ribs, for an area of about 5 cm. were resected subperiosteally from their spinal attachments to the axilla. The intercostal muscles between the ribs were divided and ligated and the intercostal musculature removed. This allowed exposure of a segment of parietal pleura, measuring about 6 by 3 cm. in diameter.

The parietal pleura was stripped down by blunt dissection from the vertebral bodies until the posterior mediastinum was exposed. Dissection was continued until the esophagus and trachea were visualized. The communicating branch of the azygos vein was at a higher level than usual and was not divided. The lower segment of the esophagus was visualized and found to be quite adherent to the trachea; it measured about 4 mm. in diameter and entered the trachea through a small communication above the bifurcation. The fistula was clamped on its tracheal side and sutured with 4-0 silk. The upper segment of the esophagus exposed and found to end blindly about 2 cm. above the distal end. Visualization of the proximal end was aided by pressure on the catheter which had been inserted into the esophagus prior to operation. The proximal end of the esophagus was about 1 cm. in diameter. Tension sutures of 5-0 silk were passed through the walls of the four quadrants of both segments of the esophagus and left untied. The proximal end of the esophagus was then opened. The catheter was passed through it down into the distal end of the esophagus and into the stomach. An end-to-end anastomosis of the esophagus was carried out by interrupted opposing sutures of 5-0 silk through the open ends of the esophagus. These were reinforced by a few mattress sutures of the same material and by the stay sutures which had first been inserted. About 0.5 Gm. of sulfanilamide powder was scattered in the posterior mediastinum, and a small rubber dam was inserted. The thoracic wall was closed with interrupted 4-0 silk sutures uniting the musculature and skin.

Prior to operation the infant had respiratory difficulty as evidenced by retraction of the thoracic wall on inspiration. There was more difficulty than usual with the anesthesia, necessitating frequent interruptions in the operative procedure. At the termination of the operation, however, the infant's condition appeared fairly good. Intravenous fluids, supplemented by a blood transfusion, were administered.

*Course:* Oxygen therapy in a cubicle, sulfadiazine, and intravenous fluids were continued. The postoperative course during the first twelve hours after operation was satisfactory, but



FIG. 6. Roentgenogram of the chest and abdomen (without the use of contrast medium) on admission showing air in the gastrointestinal tract, a catheter in the esophagus obstructed at the superior thoracic aperture, and scattered areas of consolidation in both lung fields.

soon thereafter the respirations became labored and marked cyanosis was noted. The temperature rose progressively to 105.8°F., and he died eighteen hours after operation.

*Necropsy Findings:* The incision had been made through the thoracic wall outside the



pleura. The second and third ribs had been partially removed. The wound was clean. The parietal pleura in the operative site was congested. There was no free fluid in the pleural cavities.

The esophagus, about 1 cm. above the bifurcation of the trachea, showed sutures around its entire circumference (fig. 7). A probe could be passed through the anastomosis into the



FIG. 7. Photograph of the thoracic organs at necropsy showing the site of the end-to-end anastomosis of the esophagus.

stomach. The suture line appeared intact and clean. The trachea, about 1 cm. above the bifurcation, showed on its posterior wall a funnel-shaped orifice leading into a tube which could not be probed because of closure by a silk suture next to its opening.

The other abnormal findings were bilateral bronchopneumonia of all lobes; patent foramen ovali; accessory pancreas.

*Comment:* An anastomosis of the esophagus was performed and death was due to pneumonia. At the present time, operation in such a patient would be deferred until a course of penicillin had been administered. The other congenital anomalies were not incompatible with life.

## SUMMARY

The clinical features, the surgical problems, and the results of operations for atresia of the esophagus with tracheoesophageal fistula are presented. The operation of choice is an extrapleural ligation of the tracheoesophageal fistula and restoration of the continuity of the esophagus by an anastomosis of the proximal and distal ends. This procedure was carried out in 2 patients; the infants died, two days and eighteen hours respectively, after operation, of bronchopneumonia.

## BIBLIOGRAPHY

1. ASHLEY, J. D., JR.: Congenital Atresia of the Esophagus with Tracheoesophageal Fistula. *Radiology*, 36: 621, 1941.
2. CARTER, B. N.: An Operation for the Cure of Congenital Atresia of the Esophagus. *Surg., Gynec. & Obst.*, 73: 485, 1941.
3. GAGE, M., AND OCHSNER, A.: The Surgical Treatment of Congenital Tracheoesophageal Fistula in the New-born. *Ann. Surg.*, 103: 725, 1936.
4. HAIGHT, C.: Congenital Atresia of the Esophagus with Tracheoesophageal Fistula; Reconstruction of Esophageal Continuity by Primary Anastomosis. *Ann. Surg.* 120: 623, 1944.
5. Idem: Personal communication. September 13, 1944.
6. Idem: Personal communication. October 24, 1944.
7. HAIGHT, C., AND TOWSLEY, H. A.: Congenital Atresia of the Esophagus with Tracheoesophageal Fistula; Extrapleural Ligation of Fistula and End-to-End Anastomosis of Esophageal Segments. *Surg., Gynec. & Obst.*, 76: 672, 1943.
8. HUMPHREYS, G. H.: The Surgical Treatment of Congenital Atresia of the Esophagus. *Surgery*, 15: 801, 1944.
9. LADD, W. E.: The Surgical Treatment of Esophageal Atresia and Tracheoesophageal Fistulas. *New England J. Med.*, 230: 625, 1944.
10. Idem: Discussion of article by Haight (4).
11. LANMAN, T. H.: Congenital Atresia of the Esophagus; A Study of Thirty-two Cases. *Arch. Surg.* 41: 1060, 1940.
12. LEVEN, N. L.: Surgical Management of Congenital Atresia of the Esophagus with Tracheoesophageal Fistula. *J. Thoracic Surg.*, 6: 30, 1936.
13. IDEM: Congenital Atresia of the Esophagus with Tracheoesophageal Fistula: Report of Successful Extrapleural Ligation of Fistulous Communication and Cervical Esophagostomy. *J. Thoracic Surg.*, 10: 648, 1941.
14. Idem: Discussion of article by Haight (4).
15. MIXTER, C. G.: Discussion of article by Gage and Ochsner (3).
16. O'HARE, H. A.: Imperforate Anus and Tracheoesophageal Fistula. *Pennsylvania M. J.*, 40: 914, 1937.
17. PLASS, E. D.: Congenital Atresia of the Esophagus with Tracheoesophageal Fistula; Associated with Fused Kidney; A Case Report and Survey of the Literature on Congenital Anomalies of the Esophagus. *Johns Hopkins Hosp. Rep.*, 18: 259, 1919.
18. RICHTER, H. M.: Congenital Atresia of the Esophagus; An Operation Designed for its Cure. *Surg., Gynec. & Obst.*, 17: 397, 1913.



19. ROSENTHAL, A. H.: Congenital Atresia of the Esophagus with Tracheoesophageal Fistula; Report of Eight Cases. *Arch. Path.*, 12: 756, 1931.
20. SCOTT, W. J. M.: Quoted by Heatly, C. A.: Some Problems in Esophageal Atresia. *Ann. Otol., Rhin. & Laryng.*, 45: 1122, 1936.
21. SHAW, R.: Surgical Correction of Congenital Atresia of the Esophagus with Tracheoesophageal Fistula. *J. Thoracic Surg.*, 9: 213, 1939.
22. Idem: Personal communication. June 12, 1942.
23. VOGT, E. C.: Congenital Esophageal Atresia. *Am. J. Roentgenol.*, 22: 463, 1929.

## HERNIA REPAIR

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### FOREWORD

It is a pleasure to contribute a tribute to a Moschowitz. About forty years ago Eli cut tissue sections, stained, mounted, studied and discussed them in "Dr. Prudden's Laboratory," near the top floor of "the Old P and S" on 59th Street. Hodenpyl, Larkin, "Pa" Freeborn, Hiss, Wadsworth, Miller, Wood had work rooms. Tilney, Vogel, Zinsser, Ely, Matthews, Norris, Connell, Downs, Dayton, McWhorter, Sharp, Pool, Frank, Flint, Blake, Brewer, Darrach, Dowd, Van Beuren, Eli Moschowitz and Walton Martin were frequent visitors to "Bill Clarke's" desk where "surgical pathology" at P and S started. "Edward" and "Jimmy" kept order. The pathological tissues from Roosevelt Hospital were brought there by its pathological internes. St. Mary's Hospital for Children in 34th Street and General Memorial Hospital on 103rd Street and Central Park, West, sent their specimens there.

What talk! What arguments! Eli's dissertations were priceless!

His brother, Alexis, did more than his share at the meetings of the New York Surgical Society, in those days. Not once, but many times, he told stories of hernia that needed telling. One of the things he stressed was the Transversalis Fascia. Let what follows be a tribute to the thoughts of a Moschowitz. The Moschowitz mind sought essentials.

Alexis Moschowitz contributed to the knowledge of abdominal wall herniae and their repair. He emphasized the importance of the transversalis fascia.

Though these lines use inguinal herniae as a text, their intent is to emphasize essential factors common to abdominal wall herniae of other sort.

The internal ring of the inguinal canal can be likened to the neck of a funnel into which the abdominal wall ingredients have been poured so that they come to line the canal. The result is that the structures of the abdominal wall have their representative parts lining the wall of this funnel into the inguinal canal and below. In the normal human being the peritoneal lining of the abdomen crosses the internal ring without going down it. Should there be a bulge or a little prolongation we consider it abnormal and call it a tendency towards hernia or an early, or small, hernia. There is no normal representation of the peritoneal lining in the canal or below until the tunica vaginalis is reached in the scrotum.

Next to the peritoneal lining of the abdominal wall, are the "subserous," or "properitoneal," tissues. In the canal these tissues include the spermatic artery, the vas deferens, the artery to the vas deferens, veins, lymphatics and sympathetic nerve fibres in a loose, areolar arrangement. Should a hernial sac exist, these properitoneal tissues are the tissues most intimate to it.

Outside the "properitoneal tissues" of the abdominal wall is the transversalis

fascia. Its counterpart in the inguinal canal is called "the infundibuliform fascia."

The next most external layer of the wall of the abdomen is the transversus, or transversalis muscle. Its counterpart in the inguinal canal is the fascia of the transversus, or transversalis muscle. This fascia and the infundibuliform fascia are scarcely recognizable. They are of little importance in repairing inguinal herniae.

One must avoid confusing the terms "Transversalis Fascia" and "Fascia of the Transversalis Muscle." Suture of the Transversalis Muscle or its fascia must not be confused with suturing of the "Transversalis Fascia." Suture of the transversalis fascia is the most important step of the whole operation for repair. Suture of the transversalis muscle, or its fascia, where it merges with the lower border of the internal oblique, often kills these muscles, weakens the wall, and may contribute toward the production of a new hernia.

The internal oblique muscle is next outside the transversus muscle. They fuse in their lower, inner portions to form a short tendon, to be inserted into the pubic bone, as the so-called "conjoined tendon." The term "conjoined tendon" is often used incorrectly to describe the lower edges of these two muscles before they become the "conjoined tendon," (see below). The counterpart of the internal oblique muscle in the inguinal canal, and below it, is the cremasteric fascia containing the cremasteric muscle fibres.

Outside of these muscles is the aponeurosis of the external oblique with its external spermatic fascia crossing the external inguinal ring.

Too many inguinal herniae recur after operation. The records of all our large hospitals show this. A vast literature on the subject bears witness to this fact.

A peritoneal sac, or intestine only partly lined by peritoneum, as in a "sliding" hernia, begins its "bulge" through the abdominal wall where the wall's "first line of defense" is absent or weak. It is absent at the internal ring and at other places such as the femoral canal and obturator foramen. It may be weak in the region where direct herniae occur, or at the umbilicus, or above, in the epigastric region, or at the site of operative scars.

Intra-abdominal pressure, intensified by stresses and strains of many sorts produces a "bulge" wherever the "first line of defense" is absent or weak, and the story of "great" hernial "oaks from little" bulging "acorns" begins. Persistent pressure from within push slippery viscera through the "first line of defense" into the "bulge" that, little by little, enlarges into a "hernia."

Peritoneum and perititoneal tissues offer so little restraint to evisceration that they can practically be discounted. The "first line of defense" is transversalis fascia. This is the important thing to bear in mind. Where it is absent, or weak, herniation can occur. Once a "bulge" has begun, a "wedge" has been set and started that splits abdominal walls wide open with the "hammer blows" of intra-abdominal pressure. Coughing, sneezing, hiccough, weight-lifting, pregnancy and straining to defecate, may all be thought of as "hammer blows."

If absence or weakness of the "first line of defense" be the essential factor in hernia creation, it is evident that a new "first line of defense" must be made to prevent recurrence.

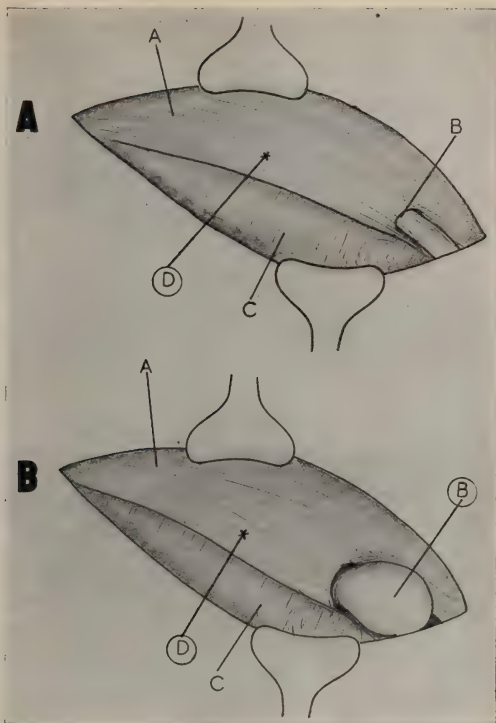


FIG. A. Appearance of the external oblique aponeurosis after the skin incision. The sac has not protruded through the external ring.

A. External Oblique Aponeurosis.

B. External Inguinal Ring.

C. Deep Fascia of the Thigh.

D. Site of the Internal Inguinal Ring. Sometimes the External Oblique Aponeurosis is relaxed and may bulge slightly where a hernia that has not protruded through the external ring exists. This is usually, however, not discernible and the presence of a Sac may not be evident until the Aponeurosis has been divided and the Cremasteric Muscle split.

FIG. B. Appearance of the External Oblique Aponeurosis where the Hernial Sac protrudes through the external ring and can readily be felt, or seen, on physical examination.

A. External Oblique Aponeurosis.

B. Hernial Sac protruding from the External Ring, showing the enlargement of the External Ring.

C. Deep Fascia of the Thigh.

D. Location of the Internal Inguinal Ring.

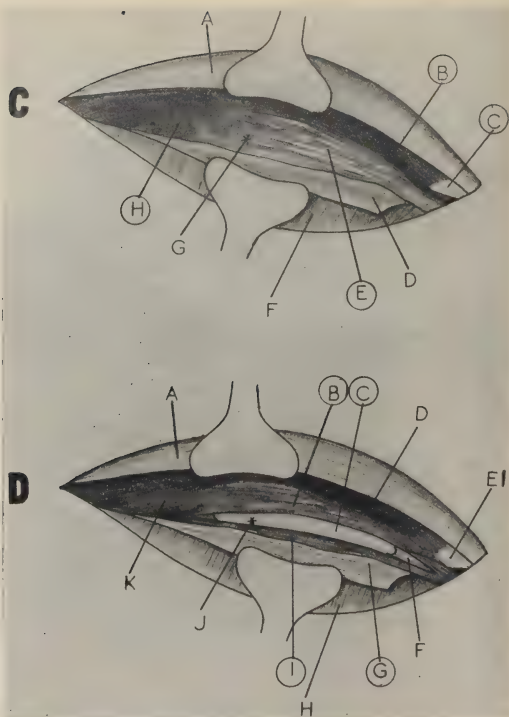


FIG. C. Internal Oblique Muscle and Cremasteric Fascia after division of the External Oblique Aponeurosis.

A. External Oblique Aponeurosis.

Ⓔ. Inner portion of Internal Oblique Muscle that at this point has begun to fuse with the Transversus Muscle to form the:—

Ⓒ. Conjoined Tendon. The term "Conjoined Tendon" has been used incorrectly for many years in descriptions of inguinal hernia. Repeatedly in these descriptions advice is given to sew the "conjoined tendon" to Poupart's ligament when it is meant to advise sewing the Internal Oblique, and the subjacent Transversus Muscle, to Poupart's ligament. The term "Conjoined Tendon" should be used to describe a short, strong tendon made by the fusion of the Internal Oblique and Transversus Muscles, running to the Pubic Spine and Linea Alba in front of the Rectus Muscle. The medial portion of the Cremasteric muscle fibres are inserted into its lower, inner margin.

D. Posterior surface of the External Oblique Aponeurosis commonly referred to as the "Shelving Margin of Poupart's Ligament."

Ⓔ. Cremasteric Muscle fibres over the hernial sac and spermatic cord, spoken of as "Cremasteric Fascia." Sometimes these muscle fibres are conspicuous and evident, —at other times, scarcely seen.

F. Deep Fascia of the Thigh.

Failure to create this "first line of defense" is the chief cause for the persistence, or recurrence, of herniae following operation. This is not done because, in the first place, its importance is not appreciated and, in the second place, a reliable technique for recognizing the transversalis fascia, i.e. the "first line of defense," has not been emphasized nor taught.

Figures A, B, C, D, E show, diagrammatically, steps in the technique of exposure of the indirect hernial sac and the search for latent weakness in the region of direct hernia. Subsequent figures F, G, H, I, J, K, L, M deal with the technique of repair.

Repair can be considered under three headings:

1. Opening and closure of the sac.
2. *Creation* of a "first line of defense."
3. *Reinforcement* of the "first line of defense."

1. Opening and closure of the sac. The sac must first be found. After dividing the external aponeurosis from the external inguinal ring, upwards and outwards along Poupart's ligament and freeing it from the internal oblique above, the "shelving margin" of Poupart's ligament is exposed by freeing it from the cremasteric fascia below by blunt dissection. The cremasteric fascia is then incised close to the deep edge of the "shelving margin." This incision is lengthened and widened by the introduction of the finger tips at either end and drawing them apart down the cord internally, and up to the origin of the internal oblique muscle externally. The "neck" of the sac is then sought. The "neck" is that portion of the sac in the canal just after its emergence from the internal ring. The "neck" is the least complicated portion of the sac. Once seen, the dissec-

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G. Site of the Internal Inguinal Ring.

Ⓔ. Internal Oblique muscle taking origin from the outer half of Poupart's Ligament.

FIG. D. The Cremasteric Fascia, with its muscle fibres, has been recognized and incised close to Poupart's Ligament. It is usually possible to identify this Fascia. Beneath this Fascia, covering the cord and the hernial sac, are two layers of fascia not so readily identified. 1. The Fascia of the Transversus Muscle. 2. The Infundibuliform Fascia. This is the funnel shaped prolongation of the Transversalis Fascia down the cord. Immediately beneath this Fascia are the Subserous, or Properitoneal tissues in which run the vessels and nerves to the Cord, the Hernial Sac and the Peritoneum.

A. External Oblique Aponeurosis.

Ⓑ. Cremasteric Muscle, or Fascia.

Ⓒ. Bulging of the Sac after the Cremasteric Fascia and the subjacent Fasciae have been divided and split apart by means of a pair of blunt scissors or the finger tips.

D. Internal Oblique Muscle.

E. Conjoined Tendon.

F. Spermatie Cord with the Vas Deferens readily identified by its little "curlicue" Artery from the Superior Vesical branch of the Internal Iliac or "Hypogastric" Artery.

Ⓖ. Shelving Margin of Poupart's Ligament.

H. Deep Fascia of the Thigh.

Ⓘ. Few fibres of the Cremasteric Muscle, or "Fascia" near Poupart's Ligament. In splitting the fibres of the Cremasteric Muscle, it is advisable to do this close to the Ligament. On the other hand, one should be cautioned against dividing these fibres too deeply, especially if the muscle and the subjacent structures have been drawn up by the operator's fingers so as to put them on the stretch. Should one divide too deeply, one might cut through the Transversalis Fascia. This might weaken it so as to create a direct hernia.

J. Site of the Internal Inguinal Ring.

K. Origin of the Internal Oblique from the Outer Half of Poupart's Ligament.



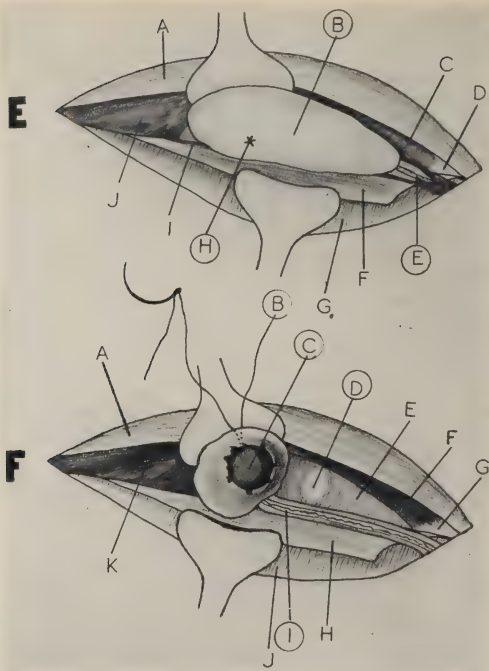


FIG. E. The Cremasteric Fascia has been so thoroughly split and disposed of that it has become almost indistinguishable from the Internal Oblique Muscle. The Sac, stripped of the fascia of the Transversus Muscle, the Infundibuliform Fascia and the Areolar, Sub-serous or Properitoneal Tissues, with their vessels and nerves, is outlined. The Cord and its Vas, well identified by its characteristic appearance, its almost wiry feel, and the so-called "curlicue" Artery of the Vas Deferens running on its surface, must be separated from the Sac. To do this, dissect close to the Sac wall, even inside its small blood vessels. This will save injury to the Cord. Aim at dissecting the sac at its "neck,"—that is, just mesial to the internal ring. Once, having completely freed the neck of the Sac, its junction with the free Peritoneal Cavity can easily be determined, and the distal portion freed and either left in, or removed.

A. External Oblique Aponeurosis.

B. Hernial Sac, ready to open so that its further dissection can be done with its wall demonstrated by fingers introduced within.

C. Internal Oblique, where it fuses with the Transversus Muscle to form the,

D. Conjoined Tendon.

E. Cord, with the Vas Deferens and its "curlicue" Artery.

F. Shelving Margin of Poupart's Ligament.

G. Deep Fascia of the Thigh.

H. Site of Internal Inguinal Ring.



tion should be carried in the properitoneal tissues around the "neck" of the sac, and as close to the sac as possible. This is the surest way to avoid injuring the vas and other cord structures. It may help, and often does, to open the sac during this part of the procedure. Whether to remove all of the sac, or leave its distal portion, requires discretion on the part of the operator. Where the sac is long and adherent, where the sac is "congenital," the lower portion may be left in. Once the sac has been dissected free to the level of the abdominal cavity, it must be emptied of its contents. If adherent, they must be freed.

At this point there is opportunity for studying the immediate interior of the peritoneal cavity for possible pathological conditions or removal of an easily delivered appendix, and the region inside the epigastric vessels for a direct hernia. The sac should then be ligated by suture or transfixion, its redundant portion cut away, and the suture passed through the transversalis and internal oblique muscles above and outside the internal ring. Here it can be sutured to the fascia covering the internal oblique muscle. This draws the closed, sac opening away from the cord at the internal ring.

2. Creation of a "First Line of Defense." The transversalis fascia must be found. This is essential to effectively close the internal inguinal ring. "The internal arcuate fibres" forming the inner edge of the internal inguinal ring are fibres of the transversalis fascia. They are the outer margin of Hesselbach's ligament. The deep epigastric vessels run upwards and inwards close to the edges of these fibres and beneath them. Were the operator to dissect the tissues to show the deep epigastric vessels, he would be more than likely to cut these "internal arcuate fibres" of the transversalis fascia that are so important to preserve.

In some instances, these fibres can be seen. Usually, however, they are not

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I. Edge of Poupart's Ligament with a few fibres of Cremasteric Fascia.

J. Origin of Internal Oblique Muscle from outer half of Poupart's Ligament.

FIG. F. The Hernial Sac has been dissected to the Peritoneal Cavity and a purse string suture taken after freeing visceral attachments to its wall. At this time it is well worth while to feel in the Peritoneal cavity for pathological possibilities and inspect, using three retractors, so as to give the best possible view.

On the right side it is frequently easy to remove the Appendix. Some surgeons think this should not be attempted. When it can readily be done, it should be done, but done carefully and without contamination. A Direct Hernia may, or may not be obvious.

A. External Oblique Aponeurosis.

B. Purse string suture about the neck of the Sac. Whether this type of purse string be used, or a single or multiple transfixion suture, varies with the size and site of the Sac. In either case, after tying a purse string or transfixion stitch of fairly strong chromic gut, the ends should be made to encircle the neck at least once, or twice in some instances, to make closure quite secure.

C. Free, Peritoneal Cavity.

D. "Bulge" suggestive of a direct hernia. Many "recurrences" of Indirect Herniae have proven to be Direct Hernia.

E. Transversalis Fascia of the "Undefended Space" of the Direct Hernia Region.

F. Internal Oblique Muscle.

G. Conjoined Tendon.

H. "Shelving Margin" of Poupart's Ligament.

I. Cord, with Vas Deferens and its characteristically conspicuous, "curlicue" Artery.

J. Deep Fascia (Fascia Lata) of the Thigh.

K. Origin of the Internal Oblique Muscle from the outer half of Poupart's Ligament.

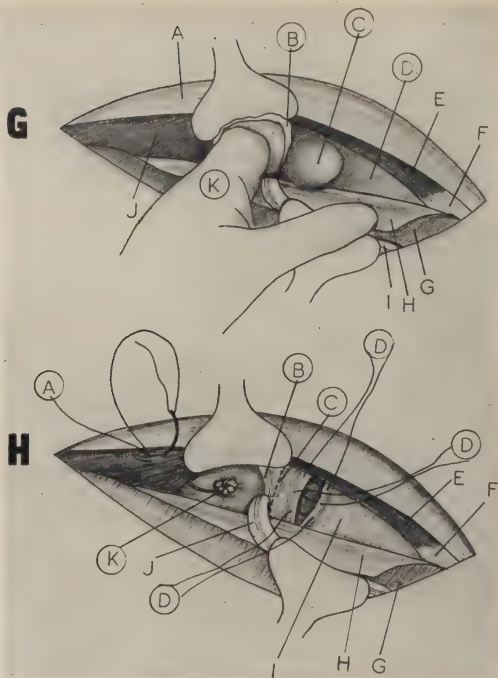


FIG. G. The neck of the Sac has been opened. The purse string suture about the Neck of the Sac is not shown. A finger is being introduced to, not only palpate the interior of the Peritoneal Cavity, but to search for a True Hernia, a "Weakness" or the "Initial Bulge" of a Direct Hernia in this so-called "Undefended Space."

A "Bulge" is here demonstrated. Sometimes, however, the "Bulge" is wholly different and may occupy the whole of the "Undefended Space" and show no evidences of strengthening, Transversalis Fascia strands. Sometimes the Bladder wall occupies part, or all, of this space. Finger introduction of this sort effectually reproduces on the operating table an "intra-abdominal tension" comparable to ordinary circumstances when the patient is up and about. In this way the early manifestation of Direct Herniae can be demonstrated.

A. External Oblique Aponeurosis.

B. Margin of the Hernial Sac.

C. Evidence of the "Initial Bulge" of a coexisting hernia in the "Undefended Space" of the Direct Hernia Region, inside the Deep Epigastric Vessels.

D. Transversalis Fascia of the "Undefended Space" of the Direct Hernia Region.

E. Inner portion of the Internal Oblique.

F. "Conjoined Tendon."

G. Deep Fascia of the Thigh.

H. "Shelving Margin" of Poupart's Ligament.

I. Spermatic Cord.

apparent. The way they can be recognized is *by feeling for them with the finger*. This technique should be cultivated in performing inguinal hernia operations. Their sharply defined margin can be felt in practically all instances if one learns how to feel for them. Figure I demonstrates the technique for finding these fibres by palpation.

Silk sutures are used to sew them to the "shelving margin" of Poupart's ligament, snugly around the cord and thus create a "first line of defense" across the internal inguinal ring.

If there be a direct hernial bulge, or true hernial sac, the edges of the defect in the transversalis fascia can likewise be felt from within the peritoneum before the closure of the indirect hernial sac. If there be no indirect hernia, after the direct hernial sac has been opened, the margins of the transversalis fascia fibres are frequently recognized by palpation. Accurate closure of such a direct hernia

J. Origin of the Internal Oblique Muscle from the outer half of Poupart's Ligament.

(K). Finger being introduced through the neck of the Hernial Sac to explore for pathological possibilities within the peritoneal cavity and study the Direct Hernia Region.

FIG. H. The Neck of the Sac has been ligated with chromic gut and the ends of the ligature passed through the Transversus and Internal Oblique Muscles so as to draw the closure away from the Internal Ring preparatory to its repair.

The inner margin of the Internal Ring is shown where the "Internal Arcuate" Fibres of the Transversalis Fascia create a sharp, *readily palpated*, but *not generally seen*, edge just outside the epigastric vessels. This is the Ligament of Hesselbach. Repair of the Internal Ring weakness by recognizing this edge and suturing it to Poupart's Ligament should be one of the chief purposes of the Indirect Hernia operation. It was a feature frequently emphasized by Alexis Moschowitz over twenty years ago. It is a step in the successful repair of an Indirect Hernia rarely performed by surgeons. It is the most important step in the whole operation, toward permanently successful repair.

Suture of the edges of a cleft in the Transversalis Fascia protecting the "Undefended Space" of the Direct Hernia region is also demonstrated.

It is the Transversalis Fascia, not the Muscles, nor the External Aponeurosis that is of prime importance in Inguinal Hernia Repair (see text).

(A). Purse string ligature of the Hernial Sac passed through the Transversus and Internal Oblique Muscles above and outside the region of the Internal Ring so as to bring the sac closure to the under surface of the abdominal wall well away from the region of the Internal Ring.

(B). "Internal Arcuate" Fibres of the Transversalis Fascia, or "Ligament of Hesselbach". Sometimes this edge can be seen. More often it cannot be. But, it can always be felt. It is a short distance outside the course of the Deep Epigastric Vessels and it can be sutured with silk sutures to Poupart's Ligament without injuring the vessels.

(C). Deep Epigastric Vessels behind Hesselbach's Ligament, which is a thickening of the Transversalis Fascia at this point.

(D). Silk sutures closing the cleft in the Transversalis Fascia of the "Undefended Space" in the Direct Hernia Region.

Direct Hernial weakness varies considerably from a vertical cleft, as depicted here, to a diffuse bulge, or real sac, with little or no recognizable Transversalis Fascia over the greater part of the Direct Hernia region.

Plication, or sutures taken from above to Poupart's Ligament, or transplantation of a fascial sheet behind the muscles, may have to be resorted to to secure an adequate "first line of defense" against such herniae (see text).

E. Internal Oblique Muscle.

F. Conjoined Tendon.

G. Deep Fascia of the Thigh.

H. "Shelving Margin" of Poupart's Ligament.

I. Transversalis Fascia of the "Undefended Space" in the Direct Hernia region.

J. Spermatic Cord with Vas Deferens and its "curlicue" Artery from the Superior Vesical Artery.

(K). Ligated neck of Hernial Sac ready for transplantation to posterior surface of Transversus Muscle.

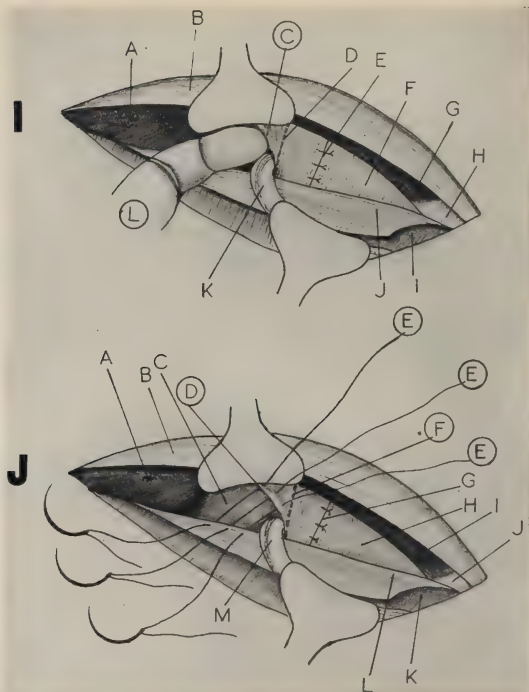


FIG. I. *Feeling for the Internal Arcuate Fibres of the Transversalis Fascia, or Hesselbach's Ligament.*

Palpation is the surest way to accurately find these fibres before suturing their edge to Poupart's Ligament.

- A. The Ligature about the neck of the Hernial Sac has been sutured to the fascia over the Internal Oblique Muscle after transplanting the closed sac orifice away from the Internal Inguinal Ring, to the posterior surface of the Transversus Muscle (see text).
- B. External Oblique Aponeurosis.
- ©. Edge of the Internal Arcuate Fibres of the Transversalis Fascia, or Hesselbach's Ligament, being palpated by the finger tip. This is, perhaps, the most essential feature in the technique of the operation.
- D. Deep Epigastric Vessels behind Hesselbach's Ligament and the Transversalis Fascia.
- E. Repair of the Direct Hernia by Closure of the Transversalis Fascia.
- F. Transversalis Fascia of the Direct Hernia Region.
- G. Internal Oblique Muscle, near its insertion.
- H. Conjoined Tendon.
- I. Deep Fascia of the Thigh.
- J. "Shelving Margin" of Poupart's Ligament.
- M. (in diagram J) The internal oblique muscle, near its insertion.

defect in the transversalis fascia, whether done from side to side, or from above downwards, should be done with silk sutures so as thus to create a "first line of defense" (figs. J, K).

Should there be an inadequate "first line of defense" in either the indirect or direct hernial regions, in other words, should the transversalis fascia be so weak or practically absent, from the standpoint of repair, the best technique for creating a new "first line of defense" is the transplantation of an adequately broad sheet of fascia from the outer side of the thigh, or elsewhere, to form a new transversalis fascia. This is a better method than the use of fascial sutures.

3. Reenforcement of the "First Line of Defense." Once an adequate "first line of defense" has been created, reenforcement is helpful. Reenforcement without the creation of a "first line of defense" is probably the cause of most of our recurrences. Reenforcement, without a "first line of defense," done in such a way as to destroy or weaken the muscle fibres (see below), used to "reenforce" with, contributes, still further, towards recurrences.

The lower edge of the internal oblique and transversalis muscles over the inguinal canal have been frequently written and spoken about as the "conjoined tendon." Many times has it been advised to suture the "conjoined tendon," meaning these muscle fibres, to the "shelving margin" of Poupart's ligament.

All over the world this advice has been given and followed. This advice is wrong.

In the first place, the lower margins of these two muscles do not become a

K. Spermatic Cord, showing the "telltale", "curlicue" Artery to the Vas Deferens so often helpful in identifying it (see text).

①. Finger, palpating the edge of the Internal Arcuate Fibres of the Transversalis Fascia so as to locate it for suture to Poupart's Ligament and thus close the Internal Ring. This is the most important step in prevention of an indirect hernia recurrence.

FIG. J. Repair of the Internal Inguinal Ring by suturing the Edge of the Internal Arcuate Fibres of the Transversalis Fascia to Poupart's Ligament with interrupted silk sutures.

A. Knot in the fascia over the Internal Oblique of the Hernial Sac ligature. This chromic ligature has been passed through the Internal Oblique and Transversus muscles above and outside the Internal Ring.

B. External Oblique Aponeurosis.

C. Peritoneum and Subserous Tissues behind the Internal Inguinal Ring.

②. The Internal Arcuate Fibres of the Transversalis Fascia, or the Ligament of Hesselbach. Suturing of this edge securely to Poupart's Ligament snugly about the emergence of the cord is the most important step in preventing recurrence of an Indirect Inguinal Hernia.

③. Silk sutures uniting the Internal Arcuate Fibres of the Transversalis Fascia to Poupart's Ligament to close the Internal Inguinal Ring and prevent the initiation of a "bulge" of peritoneum that precedes the formation of a hernia.

④. Deep Epigastric Vessels.

G. Direct Hernia Repair. This is but a diagrammatic representation of the principle of Transversalis Fascia repair. Often the repair has to be done from above downwards, or by plication, or by transplanting a fascial sheet. Fascial sutures are not as effective.

H. Transversalis Fascia of "Undefended Space" of the Direct Hernia Region.

I. Inner Portion of the Internal Oblique Muscle.

J. Conjoined Tendon.

K. Deep Fascia of the Thigh.

L. "Shelving Margin" of Poupart's Ligament.

M. Spermatic Cord.



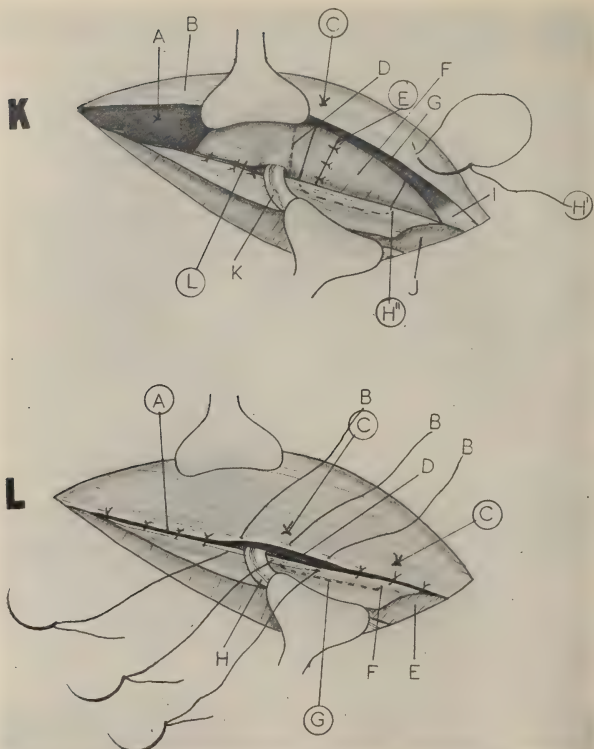


FIG. K. Repair of the Internal Ring by suturing the edge of the Internal Arcuate Fibres of the Transversalis Fascia, i.e., Hesselbach's Ligament, to Poupart's Ligament.

A method for fixing Poupart's Ligament to the posterior aspect of the Internal Oblique and Transversus Muscles so as to reinforce the Transversalis Fascia repair of the Direct Hernia region, without destroying Muscle Fibres.

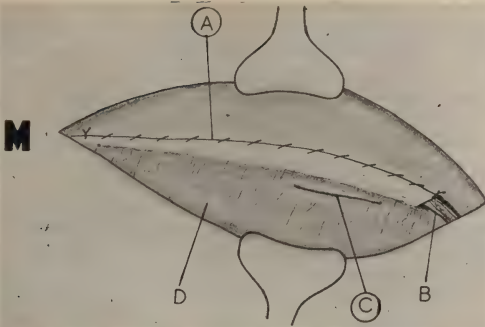
A. Suture of the Hernial Sac ligature to the Fascia over the Internal Oblique Muscle (see Fig. H.)

B. Aponeurosis of the External Oblique Muscle.

C. Outer knot of a chromic gut "Staple" suture tied in the External Oblique. This suture is to bring the shelving margin of Poupart's Ligament to the posterior surfaces of the Transversus and Internal Oblique Muscles without destroying Muscle Fibres.

The outer portion of this "Staple" suture is taken first to run less risk of injuring the femoral vessels. After knotting it to the External Oblique Aponeurosis, it is passed *directly through* the Internal Oblique and Transversus Muscles,—then, just below the edge of the shelving margin of Poupart's Ligament to and through the deep fascia of the thigh below Poupart's Ligament and returned in the reverse direction (H'') 2-3 cm. internally.

Tying a suture about a muscle is comparable to tying a suture about a bit of brain or spinal cord. Voluntary muscle fibres are one of the most highly specialized tissues of the body. The muscle cell is worthless without its nerve attachment. Suturing



of these delicate structures in such a way as to strangle them, defeats the very purpose desired.

Indeed, Bassini, in his original description of hernial repair advised suturing the fascia over the muscle and as little as possible of the muscle to Poupart's Ligament.

This "Staple" type of suture gives far better approximation with minimal trauma.

It is not an uncommon finding in operating on herniae that have been repaired by suturing the muscle to Poupart's Ligament to find black silk sutures in scar tissue and no muscle remaining. Of course, where very loose sutures have been taken, tension is lessened and such damage is less likely to occur. However, whenever stress and strain with muscle contraction occurs, tension mounts so that nerve and muscle damage does occur.

This "Staple" suture approximates Poupart's Ligament to the posterior surface of the muscles practically without constricting muscle and nerve fibres. It improves whatever transversalis fascia repair has been effected behind it.

D. Deep Epigastric Vessels.

E. Repair of Transversalis Fascia in Direct Hernia region (see fig. H.).

F. Transversalis Fascia of Direct Hernia Region.

G. Inner Portion of Internal Oblique Muscle.

H. Ending of the "Staple" Suture.

I. Conjoined Tendon.

J. Deep Fascia of Thigh.

K. Inner Portion of "Staple" Suture returning from its fixed bearing on the deep fascia of the thigh. In passing the needle from the thigh upwards beneath or through Poupart's Ligament at this point, there is no danger of harming the Femoral Vessels.

K. Spermatic Cord.

L. Repair of the Internal Inguinal Ring with silk sutures through the edge of the Internal Arcuate Fibres to Poupart's Ligament close about the emergence of the Spermatic Cord.

FIG. L. A "Staple" chromic gut suture reinforces the Direct Hernia Region.

First row of an "Overlapping" interrupted, silk suture repair of the External Oblique Aponeurosis and its "Shelving Margin" of Poupart's Ligament.

(A). Upper edge of the incised External Oblique Aponeurosis being sutured near the deep edge of the Shelving Margin of Poupart's Ligament, with:—

B. Interrupted, silk sutures.

C. Staple Suture (See Fig. K.) knotted ends.

D. Internal Oblique Muscle.

E. Deep Fascia of the Thigh.

F. "Shelving Margin" of Poupart's Ligament.

G. Staple Suture seated on Deep Fascia of Thigh.

H. Spermatic Cord, transplanted to in front of Internal Oblique and External Oblique.

FIG. M. Repair, completed.

A. Lower Margin of External Oblique Aponeurosis incision overlapped over Spermatic Cord with a continuous chromic suture.

B. Spermatic Cord.

C. "Staple Sutures" (figs. K. L.) bearing on Deep Fascia of Thigh.

D. Deep Fascia of Thigh.



tendon until it comes close to the os pubis. In the second place, suturing muscle fibres calls for a technique that will not destroy them. Sutures under tension about muscle fibres will kill them. A muscle fibre without nerve supply "dies." Sutures around delicate nerves and muscle fibres kill them. It is difficult to understand how circular sutures around muscles, even though not apparently tied tightly, can avoid tension, once the patient is up and about and subjects the muscles to stress and strain. At operations for recurrent hernia sutures that appear to have been taken about muscle fibres have often been found surrounding, not muscle fibres, but white strands of thinned out scar tissue.

Figures K and L show, diagrammatically, how a suture, tied on the external oblique aponeurosis, can be taken through the "conjoined muscles" and under the "shelving margin" of Poupart's ligament so as to draw Poupart's ligament up behind the "conjoined muscles." This provides a far more effective reinforcement of the repaired transversalis fascia without killing the muscles.

Figures L and M indicate the overlapping of the external oblique in completing the reenforcement to the "first line of defense." The cord has been "transplanted."

Recurrent hernias have not been included. Their scarred and compromised tissues present problems quite their own. Their repair calls for individualization and a variety of technique. Though not described, the underlying principles of "first line of defense" and subsequent "reenforcement" are the guides to success.

# THE DIAGNOSTIC DIFFICULTIES IN UNCOMPLICATED SYPHILITIC AORTITIS WITH A NOTE ON ROENTGENKYMOGRAPHY OF THE AORTA\*

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## INTRODUCTION

Possibly before but most certainly very soon after the initial lesion of syphilis makes its appearance the blood stream is invaded by large numbers of spirochaetes. In this way they are distributed throughout the body and deposited in all its structures and organs. The survival and further development of the *Treponema pallidum* in these disseminated foci depends on many factors concerned with the relationship between the virulence of the spirochaete and the resistance of the body. The part played by the number and concentration of spirochaetes present in any organ, and the role of the natural local tissue resistance and immunity are apparent. In this connection the phagocytic activity of special tissues like those composing the reticulo-endothelial system are of paramount importance. Undoubtedly many other forces, not thoroughly defined, are significant determinants of the extent and severity of any particular localization. It has been established that one site of invariable involvement is the root or ascending portion of the aortic arch (1). Many theories have been projected to explain this phenomenon. McMeans (2) believes that the intima of the aorta is involved mainly by direct infection from the blood stream. Others maintain that this part of the aorta contains many small vessels which are primarily affected via the hematogenous route with the production of a syphilitic endarteritis. More widely accepted are the conclusions of Klotz (3) and of Martland (4) who stress the lymphatic and mediastinal factors in the consistent involvement of the aortic root in syphilis. They visualize a massive filtration of spirochaetes out of the blood stream by the lungs during the spirochaetemia which occurs early in the infection. The lungs rid themselves of these spirochaetes by many routes, one of the most important of which is by way of their lymphatics. The pulmonary lymphatics drain into the peribronchial and mediastinal lymph nodes which quickly become infected. By further retrograde lymph flow there is a migration of spirochaetes into the peri-aortic structures. The perivascular spaces about the vasa vasorum in the adventitia become infiltrated with lymphocytes. The endothelial cells of the intima of these arterioles proliferate and finally occlusion by thrombosis occurs. Secondary involvement of the aortic media now takes place with destruction and fragmentation of the elastic fibers and fibrous tissue replacement.

Aortitis is the significant lesion of cardiovascular syphilis for it constitutes the starting point from which all other types of syphilitic heart disease arise. Extension towards the heart results in involvement of the aortic cusps with

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characteristic luetic aortic insufficiency. The sinuses of Valsalva from which the coronary arteries take their origin in the great majority of individuals are in the first part of the aorta. Encroachment on the orifices of these important vessels causes reduced coronary blood flow with the anginal syndrome, and sometimes, because of complete orificial obliteration, coronary artery occlusion. A distal extension of the aortitis may narrow the orifices of the great vessels arising from the aortic arch with similar occlusive vascular effects. Finally it can be readily understood how a diseased and weakened aortic wall may stretch and give rise to aneurism and similar distortions. It becomes clear then that the earliest and most important lesion of cardiovascular syphilis is the mesaortitis from which all other lesions spring and which, for an undetermined time, exists without any associated valvular or arterial complications. Obviously it is extremely important to determine the presence of this initial aortic involvement as early as possible (5). The diagnosis of uncomplicated luetic aortitis i.e. syphilitic aortitis without encroachment on the coronary orifices, insufficiency of the aortic valve, or aneurism of the aorta, has tried the ingenuity of clinicians since its importance was recognized.

The symptoms considered by some to be diagnostic of uncomplicated luetic aortitis are: (1) Dyspnea, occurring upon exertion or appearing paroxysmally at rest. (2) Substernal burning pain most often situated above the third costal interspace and not invariably related to exertion. (3) Cardiac insufficiency or frank failure without any other obvious etiology. All of the foregoing symptoms undoubtedly arise, from an involvement of the orifices of the coronary arteries, resulting in reduced coronary blood flow and coronary insufficiency, with eventual degeneration and scarring of the myocardium and cardiac weakness. Such symptoms are common in middle aged patients with arteriosclerotic narrowing of the coronary vessels even in the absence of syphilis. In fact Wilson (6) who correlated the symptomatology presented by 211 cases of luetic aortitis with the necropsy findings concluded that when any of the foregoing symptoms existed either an extension or complication of the luetic process or some other condition accounted for their presence. Keefer and Resnik (7) had come to a similar conclusion some years before.

Signs constantly referred to as diagnostic of luetic aortitis are (1) an accentuated tympanitic aortic second sound having a bell-like or tambour (drum-like) quality, (2) increased retromanubrial percussion dullness indicative of a widened aortic arch and (3) a systolic aortic murmur. Attention must be directed to the fact that similar signs are present in nonluetic subjects with widened or dilated aortas associated with arteriosclerosis or hypertension.

Maynard (8, 8A) and his associates who have been patient students of cardiovascular lues for many years recommend the following six criteria:

1. The undoubted evidence that the patient has syphilis.
2. The absence of any other disease that might cause aortic dilatation, viz; arteriosclerosis, hypertension.
3. The patient must be younger than 40 years of age.
4. X-ray evidence of a dilated aorta.

5. The presence of a hollow accentuated aortic second sound.
6. The possible presence of a systolic murmur at the aortic area.

It is interesting to note that Maynard's criteria are signs and not symptoms, implying that luetic aortitis is an asymptomatic condition or that symptomatology is not specific enough to be reliable. The requirements set up by Maynard and his group are extremely rigid and allow of successful identification of specific aortitis in comparatively few cases. Furthermore serological syphilis is frequently discovered for the first time in patients over 40 and the question of aortic involvement demands attention in such individuals too. Realizing the thoroughness with which the problem had been approached by previous workers our only justification for another effort to illuminate the diagnostic difficulty was the application of one new method of investigation i.e. roentgenkymography of the aorta. The rationale for utilizing this kind of study was based on speculation arising from the following known facts. The early syphilitic aortic lesion is a mesaortitis. As a result of an obliterating endarteritis of the vessels in the adventitia, the media of the aorta, which is composed mainly of elastic fibers and which possesses a minimum of muscle tissue, is very early the site of focal areas of degeneration and fibrous tissue replacement. Such changes in the anatomical structure of an artery could very well alter the elasticity of the vessel wall. Therefore it appeared to be a logical assumption that with an alteration in the elasticity of the aorta there might be a change in the character of the pulsations of the aortic wall. If this could be detected by roentgenkymography one could establish the presence of aortitis in its incipency before any of the more obvious complications appeared. This method had already proved its value in the detection of non-contractile portions of ventricular muscle resulting from previous myocardial infarctions. (Dack, Master, Sussman (9), Gubner and his associates (10).

#### MATERIAL

It is the established routine of the anti-luetic clinic to submit every patient for cardiac study before beginning therapy. In addition, patients are referred for periodic recheck of their cardiac status during the course of treatment. With rare exceptions patients in an out-patient department anti-luetic clinic have had syphilis for several years and usually have not had treatment early in the course of their infections. It was felt that the best opportunity for this study was afforded by these patients because aortitis or any syphilitic lesion localized in the cardiovascular system could be expected in greater frequency in such a group than in an earlier detected and treated group of cases. The cardiovascular status of 47 patients from those referred to the cardiac clinic from the anti-luetic clinic of The Mount Sinai Out-Patient Department were investigated in an effort to determine the presence of uncomplicated luetic aortitis. Patients who presented unmistakable evidence of undoubted syphilitic heart disease i.e. patients in whom subsequent examination disclosed definite signs or clinical evidence of aneurism, aortic insufficiency or coronary ostial involvement were not included in this study.

## METHOD

All patients were interrogated for the presence of the usual manifestations of heart disease with special emphasis on the already reviewed symptoms of aortitis. Careful physical examination was then done. Fluoroscopic visualization of the heart and great vessels and electrocardiogram were part of every patients study. One new type of observation was added, i.e. roentgenkymographic study of the aortic arch in the postero-anterior and left oblique positions. A discussion of the principles of this technique which records graphically the pulsations of the heart or blood vessels follows later.

TABLE I

*Summarizing Analysis of 47 Luetic Patients Studied for Evidence of Aortic Involvement*

|  |   |
|--|---|
| Males.....   | 32 (4 colored)  |
| Females.....   | 15 (6 colored)  |
| Age Range { Males.....                                 | 24 to 67 years  |
| { Females.....   | 23 to 63 years  |
| Average Duration of Infection.....                     | 16.1 years (Range 6 mos. to 50 yrs.). Known in 23 of 47 cases |
| Average Duration of Adequate Treatment.....            | 3.4 years. (Range 6 mos. to 10 years.)                        |
| Positive Serology at some time during observation..... | 100%  |
| Average Systolic and Diastolic Blood Pressure.....     | 133.5   |
|  | 80.3 mm. Mercury  |
| Range of Blood Pressure.....                           | 90-200  |
|  | 50-110 mm. Mercury  |
| Cases with Associated Hypertension.....                | 4 (8.5%)  |
| Cases showing Electrocardiographic changes.....        | 3 (6.3%)  |
| Cases showing Fluoroscopic findings.....               | 8 (17.6%)   |
| Cases showing Clinical Evidence of Heart Disease.....  | 2 (4.25%)   |

Table I summarizes the essential data about the 47 cases studied. Some of these features will be discussed.

## AGE, SEX, AND RACE

Interesting but not unusual were the patients of 63 and 67 who gave a history of having contracted the initial infection many years before, in one instance 50 years previously. These two patients like the great majority of the 47 cases studies were included because they manifested no definite clinical evidence of heart disease in spite of the long period of their infections. It was felt that an asymptomatic aortitis might be detected by laboratory methods. Cole and Usilton (11) observed two cases of uncomplicated luetic aortitis which appeared after the age of 65. Roughly twenty percent of the patients were Negroes with a predominance of males. Although it is a clinical observation that Negroes are more liable to suffer cardiovascular complications of lues than white persons, the relatively small number of cases considered here precluded any verification of that point.



## DURATION OF INFECTION

In 23 of the 47 cases there was an average duration of 16.1 years since the initial infection. In the other 24 cases this interval was not known. Maynard (12) showed that in syphilitic patients examined 10 to 19 years after the initial lesion, cardiovascular syphilis was discoverable in 56.8 percent of the cases. Examination after a shorter interval (4 to 9 years) revealed an incidence of 28.6 percent, while after longer intervals (20 to 29 years) 77.8 percent of patients were affected. From this standpoint the patients in our series present a fair sampling of potential cardiacs.

## WASSERMANN REACTION

All of the cases had a positive blood Wassermann reaction some time during the period of their observation and were undoubted luetics. Although patients with obvious syphilitic cardiovascular disease may have negative serologic tests in as high as 15 to 20 percent of the cases it would be extremely hazardous to attempt to identify as difficult a condition as uncomplicated specific aortitis in anyone who was not definitely a luetic. Maynard (8A) also lists positive evidence of syphilis as one of his essential criteria.

## BLOOD PRESSURE

The average systolic pressure for the entire group was 133.5 mm. Hg. with a diastolic pressure of 80.3 mm. Hg. The range of systolic pressures was from 95 to 200 mm. Hg. Four (8.5 percent) cases had systolic values over 150 and diastolic levels over 85. The common association of luetic cardiovascular disease and hypertension has been noted (13, 14). It has been maintained that the aortic disease, in some manner, perhaps by depressing the inhibitor nerves causes the elevated blood pressure. In this study where clinical evidence for the presence of cardiovascular syphilis is lacking the presence of hypertension probably indicates that the elevated pressure is unrelated to the lues and that it is of the essential type. There are no grounds for believing that the hypertension could be considered a sign of aortic involvement. This agrees with Moore's (15) conception that essential hypertension occurs in patients with aortitis with about the same frequency as in non-syphilitic patients of analogous age. However, he stated that when hypertension was present the diagnosis of uncomplicated luetic aortitis was made more successfully because it directed attention to the cardiovascular system in luetics. From our experience we are of the opinion that the presence of hypertension in syphilitic patients makes the diagnosis less secure. In fact the two cases which we suspected to have aortic involvement had an associated hypertension and this circumstance tended to invalidate the certainty of the diagnosis, for the criteria, symptomatic and objective, can be manifested equally by both conditions (16). It is of interest to note that the prognosis in luetic aortitis with hypertension is much worse and the development of the graver forms of cardiovascular syphilis is more common.



## ELECTROCARDIOGRAPHY

There were no characteristic changes produced in the electrocardiogram. With severely compromised coronary orifices the electrocardiogram may reflect the extent of the myocardial damage resulting from reduced blood supply to the heart muscle. In the 3 cases showing significant variations from the normal the presence of hypertension or the age of the patient, or both, made it a proper assumption that the electrocardiographic changes might be due to associated arteriosclerotic coronary disease. These changes consisted of RT depressions, a Q wave in the first lead, and T wave inversions in the third lead. Slurring of the QRS complex, left axis deviation and in one patient a right bundle branch block completed the alterations, which could not be considered specific in any sense. Maynard and his associates rarely found significant changes in early cases. With an associated arteriosclerosis or hypertension electrocardiographic changes were more common. Berk (17) has recently described his experiences with the use of the exercise test to bring out electrocardiographic changes in early luetics. The effect of exercise on the electrocardiogram of normal individuals casts doubt on the wisdom of drawing definite conclusions about the presence of relative coronary insufficiency and heart disease in cases where such changes are induced by exertion (18).

## FLUOROSCOPIC OR X-RAY FINDINGS

Only 8 of the 47 cases (17 percent) showed fluoroscopic or X-ray evidence of significant aortic changes which were suggestive of luetic involvement. Particular importance was attached to the presence of localized dilation of the ascending part of the aortic arch (21). Other alterations were definite and marked elongation and tortuosity of the thoracic aorta or diffuse aortic widening associated with a heart of normal size and contour. Of these 8 there were 3 who had definite diastolic as well as systolic hypertension. In these cases it was impossible to tell whether or not the changes in the aorta were associated with the elevated blood pressure. One of the 8 patients was a woman of 62 with a long history of syphilis. In spite of the long luetic history one could not be sure whether the degree of arteriosclerosis usual in the age group was not the cause of the findings. In the remaining 4 patients, 30, 38, 39, and 44 years of age, the variations in the aorta could have been considered evidence of luetic involvement. But the absence of confirmatory evidence made such an assumption hazardous.

Percussion is notably unreliable for slight degrees of dilatation so complete dependence has been placed on fluoroscopic and roentgenologic evidence of aortic widening. Many methods for determining the dimensions of the aortic root and of the ascending part of the aortic arch have been described (19, 20). Most of these employ the technique of direct measurement from standardized distance and position teleroentgenograms. Normal average dimensions have been recorded by Hampton, Bland and Sprague. They set a limit of 5.3 centimeters for the normal or for the arteriosclerotic aorta without dilatation and they were able to conclude that the ascending aorta dilated from whatever cause

measures over 6 centimeters. Their measurements were made of the transverse diameter of the aorta at its root with the patient in the left anterior oblique position. Details of their technique can be found in their paper. With laudable caution they state that even in those cases with aortic widening a final diagnosis of luetic aortitis can be made only by taking into account all the other clinical and physical findings. Edeiken (22) has shown that in teleroentgenography of the aorta considerable magnification and distortion may occur. Ingraham and Maynard (24) studied 24 young individuals with a short history of lues and no other clinical condition. Teleroentgenograms showed slight dilatation of the aorta in 6. They considered these changes within the realm of normal. Other authors deny the accuracy and usefulness of any specific numerical values and suggest dependence on fluoroscopy of the aorta and the detection of such changes as 1) elongation or tortuosity 2) widening of any portion 3) pulsation to the right of the sternum 4) increased density permitting visualization of the descending aorta—especially in patients under 50 years of age (21). Such criteria are not always valid, for many factors, both normal and pathological, influence the appearance of the aorta. In sthenic individuals with high lying diaphragms the aortic arch is compressed from below and it assumes a broad silhouette with bulging sides that can easily be confused with true dilatation. Conversely asthenic subjects possess a long narrow aortic shadow and bona fide segmental dilatations may be hidden. In the middle years of life the thoracic aorta begins to elongate and distortions in its shape result. With increasing tortuosity the aortic knob becomes more prominent and variations in the right and left borders of the aorta appear. Unless such changes are extreme and unmistakably abnormal they are difficult to interpret. Very often hypertension—even of slight degree—complicates the picture still further, for dilatation, elongation and increased tortuosity and density of the thoracic aorta result from this condition too. Where unquestionable aortic changes, particularly dilatation of the ascending portion of the arch, are seen in young syphilitic patients without hypertension the diagnosis of early luetic aortitis is justified, especially if one or more of the previously discussed signs or symptoms is present. Although the interval between an initial lesion and the appearance of aortic syphilis varies greatly aortic changes are rarely demonstrable in the younger luetics. In the middle aged group where the question most frequently arises, the physiological variations of aortic anatomy make the problem of identifying early pathological changes a perplexing one.

#### CASES WITH CLINICAL EVIDENCE OF HEART DISEASE

Only two patients complained of symptoms suggesting cardiac involvement. A 38 year old negro who had had a primary lesion 10 years before and who had been treated inadequately with Bismuth for one year complained of a "pulling down" precordial pain, dyspnea upon exertion and occasional attacks of paroxysmal dyspnea. Physical examination revealed a blood pressure of 150 systolic and 110 diastolic with a moderately enlarged heart. The second aortic sound was accentuated and had a tambour quality. Fluoroscopy con-

firmed the cardiac enlargement and disclosed a slightly dilated aortic arch. The electrocardiogram revealed a left axis deviation with RT segments depressed in leads 2 and 3 and the T wave inverted in lead 3. It was difficult not to conclude that both the symptoms and signs were associated with the hypertension. The second patient with clinical heart disease was a 55 year colored male with lues for an undetermined duration who had had a year of anti-luetic treatment. He complained of exertional dyspnea and palpitation. Examination revealed a hypertension of 200 systolic and 110 diastolic, and an enlarged heart with a "tambour" second aortic sound. Fluoroscopy showed a dilated and tortuous aorta. The electrocardiogram revealed a left axis deviation with a low T wave in lead I. Here too the hypertension and its associated phenomena could very well explain the entire clinical picture. If it is assumed for purposes of discussion that the associated syphilis was of etiologic importance, the significant fact that comes to light is that in only two (4.25 percent) of a group of 47 cases could heart disease be suspected on clinical grounds. In other words upon objective findings alone luetic aortitis in the absence of aneurysm and aortic valve insufficiency could be considered a possibility in only 2 cases. This is in contrast to the expectancy justified on pathological grounds. Warthin (23) found either macroscopic or microscopic evidence of luetic involvement of the aorta in 90 percent of 490 syphilitic patients coming to autopsy. Langer (25) reported that in a series of 23, 105 necropsies 70 to 80 percent of all luetic patients had aortic involvement. He further reported that whereas aortitis had been suspected during life in 39.3 percent of the 721 instances of luetic aortitis discovered at autopsy, it had remained undiagnosed in the remaining 437 (60.7 percent) cases. Moore, Danglade and Reisinger (26) reviewing 105 cases of pathologically proved uncomplicated luetic aortitis found that in only 4 cases was the diagnosis made before death. In 13 it had been suspected while in 52 patients the diagnosis might have been established, had a correct interpretation of the elicited signs and symptoms followed. In the remaining 46 patients either other cardiovascular conditions had obscured the luetic signs or the possibility of luetic aortic disease had not been given serious or direct attention. In a later publication Moore and Metildi (27) reported the verification of the diagnosis of uncomplicated luetic aortitis in 19.1 per cent of 115 cases in which the diagnosis was established by the application of 7 criteria they outlined. In an additional 35.6 percent of the group they noted presumptive evidence of the correctness of the original diagnosis. In contra distinction to our own experiences they concluded that an accurate diagnosis of uncomplicated luetic aortitis could be established in a considerable proportion of patients with late syphilis.

Undoubtedly there were many more instances of aortic syphilis in our 47 patients than the 2 described above. Yet on purely clinical grounds, with the aid of carefully taken histories, complete physical examination, supplemented by fluoroscopic and electrocardiographic study the diagnosis was justified only in the limited number. It is obvious from this alone that additional diagnostic aids are necessary.

## ROENTGENKYMOGRAPHY OF THE AORTA

Roentgenkymography is a method of recording the movements of the actively beating heart and pulsating aorta on an X-ray film. This is done by interposing a lead grid between the X-ray film and the subject. The lead grid is fenestrated by horizontally placed slits 0.4 mm. wide, spaced 12 mm. apart, allowing X-rays to fall on the films through the open slits. In this way narrow transverse segments of the beating heart and aorta are recorded on the X-ray film and pulsations at respective levels on the right and left borders of the heart are visualized. The film is automatically moved down for distance equal to a little less than the slit separation distance (12 mm.) during an exposure period of from 1 to 2 seconds, thereby recording, at normal heart rates, two or three cardiac cycles. For complete technical details reference can be made to the writings of Stumpf (28) and of Hirsch (29). The films obtained by this method show, on the borders of the heart, a series of waves of varying depth, dependent upon the extent of systolic contraction and diastolic relaxation at any level. Ventricular systole is recorded as a straight horizontal inward thrust while ventricular diastole is reflected as a curved outward excursion. The auricular contractions have a characteristic appearance as do pulmonary artery and aortic curves of the heart border. The diagnosis of myocardial infarctions, ventricular and aortic aneurysms, dilated chambers in varied types of valvular disease, pericardial lesions, solid neoplasms of the mediastinum, etc. is aided by this method of X-ray visualization (30, 31, 32). It was with the idea of detecting early variations in aortic pulsations that kymograms in the postero-anterior and left oblique positions were taken in these 47 patients with a luetic infection and no clinical evidence of aortitis. In brief it can be stated that kymography of the aortic arch for the early detection of luetic lesions is disappointing as a diagnostic aid. There are many reasons for this. The aorta, so closely attached to the heart, and subject to the influences of so actively contracting an organ, shares in the movement of each cardiac contraction. Not only does the aorta pulsate expansively with each ventricular systole and diastole but it also moves en masse with each cardiac contraction. The degree of intrinsic pulsation and of en masse movement are variables determined by many factors among which are: 1. The blood pressure, 2. The age of the patient and the consequent degree of arteriosclerotic vessel changes, 3. The force of the myocardial thrust, the stroke volume, and the cardiac rate, 4. The size of the heart, 5. The position of the diaphragms, 6. The phase of respiration, 7. The interfering effect of adhesions from previous mediastinal or hilar infections. Because of the number of varying factors it is extremely difficult to establish standards of aortic pulsation sufficiently well defined and constant to allow the detection of the minimal variations which would have interested us. Furthermore early luetic changes are found most often in the intra-ventricular portion of the ascending part or root of the aortic arch. In many cases, this part of the aorta could be poorly visualized, even in the oblique position. Diagnostically helpful kymograms of the aorta have been described in outspoken luetic aortic insufficiency or aneurysm but in such cases

a clinical diagnosis is relatively easy and makes this type of X-ray study unnecessary. The difficulties encountered with kymography of the aorta in early luetic aortitis are analogous to the already established shortcomings of the fluoroscopic or simple roentgenographic study of the aorta for uncomplicated early aortitis. There too the normal variations of aortic size and contour diminish the possibility of ascertaining the minimal deviations which would indicate an incipient pathological state. As a result of this study it can be stated that roentgenkymography of the aorta is of no help in the detection of simple aortitis in luetic subjects without clinical signs or symptoms.

Perhaps from the recent perfection of the direct visualization in vivo of the cardiac chambers and great vessels with intravenous Diodrast (33) will come a method for measuring accurately the size of the aorta both in normal and abnormal states.

#### SUMMARY

Forty seven patients with positive serological evidence of syphilis were studied for evidence of cardiovascular involvement. These subjects were a mixed group including men and women of all ages. Some had acquired their infections comparatively recently while others in the group gave a history of having been infected many years before. All were under treatment and had been receiving anti-luetic therapy for varying periods of time. None presented symptoms or signs of outspoken or advanced cardiovascular syphilis, such as aneurysm, aortic insufficiency or coronary artery orifice narrowing. The exclusion of such cases was intentional for they present no unusual or exceptionally difficult diagnostic problem. Signs or symptoms that would lead to a justified diagnosis of uncomplicated luetic aortitis were particularly sought for. The criteria of the Cooperative Clinical Group with modifications suggested by Maynard and his co-workers were used as guides. In addition to careful questioning and examination each patient was further studied by fluoroscopy of the chest, electrocardiography, and roentgenkymography of the aorta. All the data were assembled and analyzed for a final evaluation of the validity of the diagnosis of uncomplicated luetic aortitis. In only 2 of the 47 patients was such a diagnosis warranted. It was recognized that in the light of the higher incidence of luetic aortitis (60-80 percent) reported in necropsy studies of luetics, many cases of specific aortitis in this series were undetected. The additional method of study employed here—roentgenkymography of the aorta—gave no assistance. The difficulty of establishing normal standards of visualized aortic pulsation made interpretations impossible. A multitude of varying factors made the problem of determining a normal kymographic picture of the aorta at different age periods etc. an extremely difficult one. Similar obstacles surround the question of establishing normal limits for the dimensions of the aorta when studied fluoroscopically or roentgenologically.

#### COMMENT

It is apparent that simple luetic aortitis is a clinically elusive condition. Symptomatology is not specific and objective data are made unreliable by the



difficulty of establishing normal standards for aortic size and pulsation. Perhaps the only set of circumstances which justifies a definite diagnosis is the visualization of an unmistakably dilated aorta—particularly if the widening involves the ascending portion of the arch—in the luetic patient without hypertension whose age and general condition would preclude the possibility of ascribing the aortic change to arteriosclerosis.

Realization that uncomplicated luetic aortitis is virtually impossible to detect in vivo and in the light of the knowledge that it exists frequently in syphilitic subjects, should encourage the attitude that it is justifiable, for the benefit of the patient, to hazard the diagnosis on less than perfect grounds. Furthermore because of the esoteric nature of the diagnostic criteria the condition cannot possibly be discovered in any but known luetics. Fortunately syphilis is detectible by a simple blood test which should be applied to all patients who seek medical attention. Only by adopting these viewpoints will it be possible to discover incipient cardiovascular lues and to deal with uncomplicated luetic aortitis, the initial lesion of all other forms of syphilitic heart disease, in a manner which its importance and seriousness deserves.

#### CONCLUSION

Early luetic aortitis, before the occurrence of coronary artery orifice involvement, aortic insufficiency or aortic aneurysm, is clinically undetectable. Exceptionally it may be diagnosed when specific signs are found in a young luetic who has neither arteriosclerosis or hypertension. Uncomplicated specific aortitis is an asymptomatic condition. Symptoms imply an extension or complication of the syphilitic process in the aorta. Roentgenkymography of the aorta is of no aid in the early discovery of uncomplicated luetic aortitis. In view of the high incidence of uncomplicated luetic aortitis established by necropsy studies it must be recognized that though undiagnosable it is often present in known luetics.

#### BIBLIOGRAPHY

1. SAPHIR, O., AND SCOTT, R. W.: *Am. Heart J.*, 6: 56, 1930.
2. McMEANS, J. W.: *Am. Heart J.*, 6: 42, 1930.
3. KLOTZ, O.: *Tr. Am. Physicians*, 1917.
4. MARTLAND, H. S.: *Am. Heart J.*, 6: 1, 1930.
5. THOMPSON, W. P., COMEAU, W. J., AND WHITE, P. D.: *Am. Heart J.*, 17: 286, 1939.
6. WILSON, R.: *Am. J. Sc.*, 194: 178, 1937.
7. KEEFER, C. S., AND RESNIK, W. A.: *Arch. Int. Med.*, 37: 264, 1926.
8. MAYNARD, E. P. ET AL.: *Brooklyn Hospital J.*, 2: 69, 1940.
- 8a. MAYNARD, E. P.: *Modern Concepts of Cardiovascular Disease*, 11: 12, 1942.
9. DACK, S., SUSSMAN, M. L., AND MASTER, A. M.: *Am. Heart J.* 19: 453, 1940.
10. GUBNER, R., AND CRAWFORD, J. H.: *Am. Heart J.*, 18: 8, 1939.
11. COLE, H. N., AND USILTON, L. J.: *Arch. Int. Med.*, 57: 893, 1936.
12. MAYNARD, E. P.: *Arch. Int. Med.*, 55: 873, 1935.
13. SCHERF, D., AND BOYD, L. J.: *Cardiovascular Diseases*, St. Louis, Mosby, 1939.
14. SCHLESINGER, H.: *Handbuch der Haut und Geschlecht Krankheiten (Jadassohn)* bd. 16, pt. 2, p. 272.
15. MOORE, J. E., AND METILDI, P. F.: *Arch. Int. Med.*, 52: 978, 1933.



16. PURKS, W. K.: *Am. Heart J.*, 9: 660, 1933.
17. BERK, L. H.: *New York State Med. J.*, 41: 223, 1941.
18. RISEMAN, J. F., WALLER, J. V., AND BROWN, M. G.: *Am. Heart J.*, 19: 683, 1940.
19. HAMPTON, A. O., BLAND, E. F., AND SPRAGUE, H. B.: *Am. Heart J.*, 6: 77, 1930.
20. VAQUEZ, H., AND BORDET, E.: *The Heart and Aorta*: New Haven, Yale Univ. Press, 1920.
21. KURTZ, C. M., AND EYSTER, J. A.: *Am. Heart J.*, 13: 67, 1937.
22. EDEIKEN, J.: *Am. Heart J.*, 20: 77, 1940.
23. WARTHIN, A. S.: *South. M. J.*, 24: 293, 1931.
24. INGRAHAM, R., AND MAYNARD, E. P.: *Am. Heart J.*, 6: 82, 1930.
25. LANGER, E. MUNCHEN: *Med. Wchnschr.*, 73: 1782, 1926.
26. MOORE, J. E., DANGLADE, J. H., AND REISINGER, J. C.: *Arch. Int. Med.*, 49: 753, 1932.
27. MOORE, J. E., AND METILDI, P. F.: *Arch. Int. Med.* 52: 978, 1933.
28. STUMPF, F., WEBER, H. H., AND WELTZ, G. A.: *Roentgenkymographische Bewegungslhre innerer organe*. Leipzig, 1936 g. Thieme.
29. HIRSCH, I. S.: *Radiology*, 22: 403, 1934.
30. WOOD, F. G.: *Lancet*, 1: 249, 1939.
31. GUBNER, R., CRAWFORD, J. H., SMITH, W. A., AND UNGERLEIDER, H. E.: *Am. Heart J.*, 18: 729, 1939.
32. DACK, S., SUSSMAN, M. L., AND MASTER, A. M.: *Am. Heart J.*, 19: 464, 1940.
33. ROBB, G. P., AND STEINBERG, I.: *Am. J. Roentgenol.*, 41: 1, 1939.

# CONTINUOUS IMMOBILIZATION OF BOTH LUNGS BY AIR PRESSURE AND ITS APPLICATION TO THE TREATMENT OF PULMONARY TUBERCULOSIS

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Inhalational therapy has modified in various ways the breathing pattern of patients with disturbances in respiratory function. In clinical dyspnea due to anoxia the inhalation of oxygen-enriched atmospheres has been shown to result in a decrease in the volume of breathing. When increased percentages of carbon-dioxide are inspired, the pulmonary ventilation is progressively increased. The inhalation of helium with oxygen is responsible for a decrease in the physical effort of breathing in conditions characterized by obstruction in the respiratory passageway. The volume of breathing may or may not be lowered, but the effort is diminished. During positive pressure respiration the physical effort of breathing is also decreased in obstructive dyspnea when it is applied during inspiration or both cycles of respiration, and the total pulmonary ventilation is often diminished. The employment of positive pressure in expiration only is designed for the treatment of pulmonary edema and is less apt to result in noteworthy changes in the amount of air or oxygen breathed. Under the latter condition there is increased work on the part of the patient who breathes outward against an arbitrarily imposed obstruction.

Cessation of all lung movement may be temporarily produced by hyperventilation with pure oxygen, which reveals the importance of the chemical regulation of breathing. A normal individual may show a cessation of all chest motion for a period as long as 5 minutes without discomfort or signs of anoxia.

The purpose of this communication is to describe a method of producing continuous arrest of lung movement and at the same time provide a normal pulmonary ventilation with an adequate exchange of oxygen and carbon-dioxide between the pulmonary epithelium and the alveolar air. In 1926 Thunberg constructed a respirator, which he called the barospirator, in which an alternating pressure of one-sixth of an atmosphere was produced 25 times a minute. A person enclosed in this chamber obtained an adequate pulmonary ventilation with little change in the volume of the chest (1). The device was employed to maintain artificial respiration in patients with poliomyelitis in whom respiratory paralysis had taken place. The principle of this method depends on the physical law that the number of gas molecules in a container, with the volume and temperature constant, varies with the degree of pressure to which the gas is exposed. Thus, if the lungs hold 3000 cc. of air at the end of a normal expiration increasing the pressure one-sixth of an atmosphere would result in an increase in the number of gas molecules present in them equivalent to 500 cc. Similarly, when the pressure change was decreased one-sixth of an atmosphere there would be a diminution in the number of molecules in the lung of approxi-

mately 500 cc. If one were to assume a rigid container, as Thunberg did, no change in the size of the container would naturally take place. Although Thunberg observed little or no movement of the chest wall in normal subjects, our studies soon revealed a slight initial compression of the chest which took place when the positive pressure wave was applied to the thorax and, conversely, a slight expansion of the chest wall during the negative pressure phase. When patients with pulmonary disease were exposed to an alternating pressure of one-sixth of an atmosphere, expansion of the chest during the negative cycle was quite marked, as well as the subsequent compression of the chest during the height of the positive pressure wave. The degree of alternate enlargement and contraction of the thorax varied with the extent of resistance in the tracheo-bronchial passageway. It was evident that the Thunberg barospirator could not be used for the treatment of patients with pulmonary tuberculosis since our object was complete arrest of lung movement.

Since the walls of the thoracic cage are somewhat flexible, the project of immobilizing them required that an equal pressure be exerted on the outer and inner surface of the chest wall (and on the upper and lower surface of the diaphragm) at precisely the same moment. Since the air which enters the lung, which ultimately builds up a pressure on the upper surface of the diaphragm and on the inner surface of the chest, must pass through the pharynx, larynx, trachea, and the large and smaller bronchi, a certain time interval is necessarily present during which a higher pressure is applied to the external surface of the thorax than to its inner surface. The problem resolved itself into a method of delaying the application of pressure to the outer chest wall until the time of the arrival of an equivalent pressure within the lung. As a result of experimental and clinical investigation, it became apparent also that in most subjects 5 cm. pressure was consumed by the tracheo-bronchial resistance in the passage of air from the pharynx to the lungs.

At first the body of the patient was surrounded by a box, with closure at the neck, and the patient and this box were then placed into a large room in which an alternating pressure of 55 mm. Hg above and below the atmosphere was obtained. By adjusting the number of holes in the inner box the pressure, as well as the time of arrival of pressure on the outer chest wall, could be made equivalent to that which entered the lung through the nose. Later a transportable type of chamber (fig. 1) was developed in which this object was obtained by first passing the air into the head end of the chamber and then, through a slightly constricted orifice, into the body end of the chamber. In this way a slightly smaller total pressure was applied to the chest wall at a slightly later moment in time than that which was applied to the nose or mouth of the patient. This chamber, which we call the equalizing pressure chamber, accomplishes normal or increased pulmonary ventilation without movement of the chest wall or diaphragm.

Complete arrest of spontaneous respiration is obtained in patients after a little preliminary training. At first, the impulse to breathe recurs in cases of pulmonary tuberculosis who are treated by this method of providing local lung

rest. However, when the chemical requirements of the body are met by an adequate supply of oxygen and elimination of carbon-dioxide, the impulse for spontaneous respiration ceases. This arrest of voluntary breathing can only be made continuous if the pressure on each side of the chest wall and the diaphragm is made equal. When the pressure is allowed to arrive at the chest wall before adequate delay has been accomplished there appears to be a cumulative compression of the chest. Expressed differently, when alternating pressure is used without the differential resistance which equalizes the pressure relationships, being maintained, a feeling of increased compression of the chest takes place which ultimately forces the individual to take an inspiration. Continuous immobilization of the lungs therefore can only be maintained when the pressure

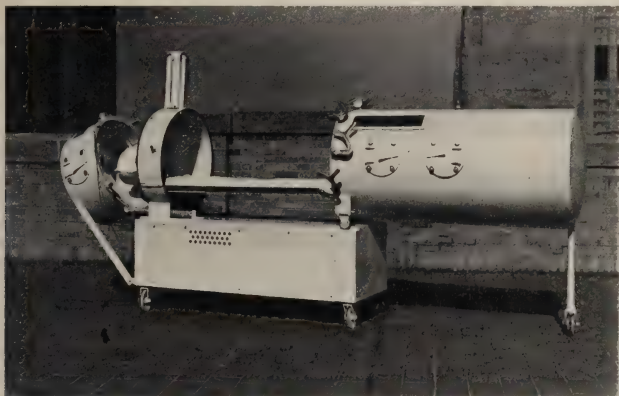


FIG. 1. Equalizing pressure chamber open

on each side of the chest wall has been made equal and in addition an adequate exchange of gases in and out of the lungs be provided.

In animal experiments in which asphyxia was produced by excessive doses of nembutal, the use of the barospirator principle, namely, alternating pressure, was unable to maintain respiratory function. A gradual increase in carbon-dioxide and a progressive lowering of the oxygen saturation of arterial blood was found. When equalizing pressure was added under the same circumstances, the animals showed maintenance of normal respiratory function, without significant lowering of the arterial oxygen saturation or retention of  $\text{CO}_2$  (2).

The equalizing pressure chamber was developed in order to provide complete lung rest in patients with pulmonary tuberculosis. Individuals who reside in this chamber also obtain an unexpected form of body rest. One of the remarkable effects of arrest of voluntary breathing is the type of bodily relaxation

which is observed when the effort of breathing is performed by the machine and not by the patient. An individual who is in such a chamber without the apparatus in use reveals the same restlessness and movement of hands or legs seen in the patient who is at bed rest. However, as soon as the breathing is taken over by the application of equalizing pressure, the impulse for spontaneous movement of the hands and legs is strikingly diminished. In some instances a patient will lie for 4 hours without turning or manifesting any change in body contour. The desire to smoke cigarettes which patients show at ordinary bed rest is much less or almost absent when breathing is performed by the chamber. As a result of cessation of normal respiration, a degree of body rest is obtained which is not possible during ordinary bed rest. No patient has been encountered who could lie quietly in a bed for long periods when normal breathing was taking place. The employment of continuous immobilization of both lungs, with provision of an adequate pulmonary ventilation, makes possible both a degree of local lung rest and body rest not hitherto available.

The application of this type of therapy has been undertaken in 10 patients with advanced pulmonary tuberculosis. The patients generally reside in the chamber from 8:30 in the morning until 9:30 or 10 o'clock at night, and are only removed at meal time. A course of therapy of four months duration has arbitrarily been selected. The preliminary results of a series of 5 patients revealed marked improvement in 4 of them (3). Of the 10 patients who have been treated with one or more courses of immobilizing lung therapy, 3 of them have been classified as being either little improved or transiently improved, without significant alteration in their course. A fourth patient showed a collapse of a large cavity in the left lung with a recurrence on slight activity; this patient is now being treated in a second course. Of the remaining 6 patients, 5 of them have been discharged as able to work and in 4 in whom a follow-up has been possible, all are at work without signs of active disease. In some there has been a complete clearing of tuberculous lesions and cavities, and in others there has been complete arrest of the disease, with evidence of fibrosis on x-ray examination. The sixth patient who showed marked improvement was ambulatory for a period of two years but is now in a municipal institution and reveals on x-ray examination what appears to be a small cavity at the site of his original large lesion. His sputum has been and is now consistently negative since the second course of treatment and he is in apparent good condition, manifesting no signs of clinical tuberculosis, except the area of apparent cavity on x-ray.

Two of the patients who have shown a favorable outcome as a result of this treatment had one course of treatment. Three patients had two courses of approximately 4 months each and one patient had three courses of treatment before all signs of the disease cleared and before the cavities in both lungs were completely absent. The seventh patient will have had two courses of treatment.

The mechanism by which clearing of advanced tuberculous disease is accomplished in this chamber may be discussed provisionally. Local lung rest inevitably decreases the diffusion of toxins from the tuberculous lesion. There is a striking diminution in the impulse to cough, which also makes less likely a



spread of the disease. Since arrest of lung movement is begun at the conclusion of a normal expiration, the elastic tension of the lung is at a minimum. A specific factor in causing collapse of cavity is in all probability the removal of the ball-valve mechanism which is commonly responsible for enlargement and maintenance of tuberculous cavities. Thus, in ordinary breathing, an inspiration is accompanied by an enlargement of the cavity and, when the respiratory passageway between the cavity and the bronchi is small, by a decreased rate of emptying of the cavity, with a consequent pressure on its walls. Since there is no movement of the cavity as long as there is a passageway between it and the bronchi during immobilizing lung therapy, this alternate modification of the size of the cavity does not take place. When arrest of lung movement is provided by equalizing pressure therapy, there is a passage of air into the cavity during the positive phase and an exit of air from the cavity during the negative phase. As long as some opening exists between the cavity and the bronchi this interchange of air results without compression of the walls of the cavity. It is possible that in cavities of very large size the diameter of the bronchus leading to the cavity may be so small in relation to the total size of the cavity as to result in some compression and expansion of the cavity during the phases of positive and negative pressure. In two of the cases in which no significant improvement took place the very large size of the cavity may have been responsible for a situation in which complete absence of movement of their walls was not secured. In one of these patients an evening temperature of  $104.5^{\circ}\text{F}$ . on admission to the hospital represented the terminal stage of a bilateral confluent type of tuberculosis.

In the presence of cavities of moderate size the cessation of lung movement obviously prevents the inspiratory enlargement of the cavity which necessarily takes place during ordinary breathing. That this type of local lung rest has a specific effect in producing collapse of cavity has been demonstrated in an unquestionable way. In a number of patients in this series, a cavity has disappeared during the first course of treatment only to reappear after discharge from the hospital during convalescent care. A subsequent course of treatment resulted in complete closure of the cavity in the same length of time as was required during the first course. This type of evidence shows the specific effect of local lung rest as provided by immobilizing lung therapy in achieving the closure of cavity as well as the clearing of infiltrative lesions (4).

During the course of this therapy gain in weight was sometimes striking, as much as 35 pounds in three months. The cough and expectoration are notably decreased in a period of 2 or 3 weeks. In fact, there is not infrequently on x-ray examination signs of scattered atelectasis as the result of the decreased cough and therefore diminished ventilation of certain areas of the lung. Although the patient is quite able to cough in the chamber and could be instructed to expectorate the secretions which accumulate during the absence of normal breathing, our procedure has been to suggest no postural drainage or no deliberate coughing in order to keep lung rest at a maximum. The possibility presents itself, however, that emptying of the cavity by deliberate coughing may be de-



sirable. There is one other characteristic of this type of therapy that may be mentioned, namely, the effects on the eardrums of the alternating pressure. In all the patients that have been treated this sensation, which may be uncomfortable at first, is one to which they become oblivious, generally within 2 or 3 days. However, our more recent custom is to place sponge-rubber containers over each ear in order to make the sensation minimal.

Patients have not found this treatment uncomfortable or burdensome. In every instance in which the disease of the patient recurred after the first course of treatment, the patient urgently requested another course of therapy. In some instances thoracoplasty had been advised when one lung cleared under immobilization therapy, but the patient invariably expressed the desire for a second course in order to have the opportunity for complete arrest of the disease without thoracoplasty.

#### SUMMARY

A method of continuous immobilization of both lungs by air pressure is described. The principle of alternating pressure, originally reported by Thunberg, accomplishes an adequate ventilation of the lung but does not provide arrest of lung movement. An alternating pressure of one-sixth of an atmosphere results in compression and expansion of the chest during the positive and negative pressure waves respectively in patients with pulmonary tuberculosis.

The development of a method of immobilizing the chest wall and diaphragm, with the production of complete arrest of lung movement, was made possible by decreasing the pressure applied to the chest wall through enclosing the body of the patient in a separate chamber from that of the head. At the same time the pressure applied to the thorax was delayed for a moment of time until an equivalent pressure passed through the tracheo-bronchial passageway to the inner surface of the chest.

The application of local lung rest in the equalizing pressure chamber was employed in 10 patients with advanced pulmonary tuberculosis. In 6 patients a significant improvement took place. The seventh patient is still under treatment. Five patients have been discharged as able to work and reveal either no evidence of tuberculous disease or complete arrest of disease; these five patients have been clinically well for periods of 1 to 4 years and in 4 in whom follow-up has been possible all are at work.

The procedure has been employed up to this time on patients in whom no other form of therapy was available. Pneumothorax had either been tried or was considered unsuitable and the bilateral nature of the disease precluded thoracoplasty except in one patient in whom a double thoracoplasty had been advised.

When voluntary respiration is dispensed with and the physical effort of breathing is no longer present in the chamber, a special type of relaxation takes place in which the impulse for movement of the voluntary musculature is either strikingly diminished or absent. Patients are able to lie for hours at complete body rest in the chamber although at ordinary bed rest this type of complete physical immobility is impossible to maintain.

Immobilization of both lungs by this type of equalizing air pressure has been shown to have a specific effect not only on the clearing of infiltrative, tuberculous lesions, but also on the collapse of cavity.

#### BIBLIOGRAPHY

1. THUMBERG, T.: The barospirator: a new machine for producing artificial respiration. *Skandinav. Arch. f. Physiol.*, 48: 80, 1926.
2. BARACH, A. L.: Immobilization of lungs through pressure. *Am. Rev. Tuberc.*, 42: 586, 1940.
3. BARACH, A. L.: Continuous arrest of lung movement. Treatment of pulmonary tuberculosis in an equalizing alternating pressure chamber. *Am. Rev. Tuberc.*, 43: 56, 1941.
4. BARACH, A. L.: Principles and Practices of Inhalational Therapy, Philadelphia, J. B. Lippincott Co., 1944.

# MULTIPLE PURULENT ARTHRITIS DUE TO MENINGOCOCCUS IN VERY EARLY INFANCY

REPORT OF A CASE IN AN INFANT SUFFERING FROM CONGENITAL CATARACT AND CARDIAC DISEASE WHOSE MOTHER HAD RUBELLA DURING FIRST MONTH OF PREGNANCY

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The newborn infant whose history follows is of interest for the following reasons: During the first month of pregnancy the infant's mother suffered from an attack of German measles. The infant was born with two congenital deformities, a cataract in the right eye and a cardiac lesion. The relationship of these deformities to the mother's previous illness will be only briefly discussed as the ocular findings in this infant have already been published by Dr. Algernon Reese who operated on and reported this case together with two other similar cases under the title "Congenital Cataract and Other Anomalies Following German Measles in the Mother" (1). At the age of six weeks the infant developed an acute febrile illness characterized by purulent arthritis in several joints aspiration of which yielded a pure culture of meningococcus. The infant made an excellent recovery.

## CASE REPORT

*History:* R. S. (Adm. # 515748), aged 7 weeks, was admitted to The Mount Sinai Hospital on January 23, 1944 because of dyspnoea and lack of appetite. He was the first child of healthy parents. During the first month of pregnancy the mother had suffered from an attack of German measles. Delivery was by forceps at full term after an 18 hour labor. The birth weight was 6 pounds. At the age of four days cyanosis was first noted and a diagnosis of congenital heart disease was made. Examination also revealed a cataract of the right eye and a right palpebral aperture slightly smaller than the left. At the request of his pediatrician, Dr. Erich Siegel, he was seen by one of us two weeks later and it was decided that on account of his small size and general debility he should be kept in the infants nursery of the hospital for several weeks more. He was visited by his father and by an uncle, both of whom were soldiers stationed at an army camp. At the age of six weeks the infant developed purulent conjunctivitis of the right eye which lasted about two days and was followed by pharyngitis, cervical adenitis, low grade fever, mild dyspnoea and anorexia. The last two symptoms persisted until admission to The Mount Sinai Hospital when the infant was 7 weeks old.

*Examination:* On admission the temperature was 99.2°F. The weight was 7 pounds 8 ounces. The infant appeared ill. He was somewhat dyspnoeic and his color was dusky. Ears, nose and throat were normal. In the right eye there was a dense white cataract which occupied the entire pupillary area. The pupil reacted slightly to light. The cornea and iris were normal. The right eye appeared slightly smaller than the left. Examination of the left eye revealed the cornea, iris and lens to be normal and the pupil reacted promptly to light. The left fundus examination showed a grayish-white disc with clear margins. The peripapillary region was depigmented. In the lower temporal quadrant and less so in the nasal quadrant the pigment was irregularly distributed. The heart was enlarged and a loud rough systolic and a short blowing diastolic murmur were heard loudest at the base and along the sternum. The lungs were normal. The liver was felt two fingers

breadth below the costal margin. The spleen was just palpable. The right kidney was palpable and seemed enlarged. Neurological examination was negative. The fontanelle was flat.

*Laboratory data:* On admission: hemoglobin, 74 per cent; red blood cells, 3,700,000; white blood cells, 37,600 with segmented polynuclear neutrophils, 41 per cent; non-segmented, 30 per cent; lymphocytes, 23 per cent; monocytes, 6 per cent. The cells showed moderate toxic granulation. Urine normal. The Wassermann, Patch and Mantoux tests were negative. A throat culture disclosed *Streptococcus viridans* A, *Staphylococcus albus* B and *Staphylococcus aureus* A. A nose culture showed *Staphylococcus albus* B. X-ray examination of the chest revealed enlargement of the heart, both at the base and in its transverse diameter. Electrocardiography showed right axis deviation and a polyphasic QRS in the standard leads. Phonocardiogram revealed a crescendo systolic murmur of very high amplitude closely followed by a decrescendo diastolic murmur of moderate amplitude. The murmurs were loudest below the pulmonary area.

*Course:* On the second day after admission the child's temperature rose to 103°F. and ranged from 100°F. to 104°F. for the following eight days. On the fourth day after admission fluctuant areas were noted over both ankle joints. Aspiration of the swelling below the left external malleolus revealed pus. Attempts to do femoral punctures to obtain blood for culture yielded pus from both sides which was apparently aspirated from the hip joints. Culture of this pus and also a blood culture revealed meningococcus type 1. Spinal tap at the same time produced normal spinal fluid. Roentgenograms of the lower extremities failed to show osteomyelitis. A small dose of Antimeningococcus serum was injected intramuscularly without untoward effect and a mixture of the serum diluted with an equal part of normal saline solution was injected slowly intravenously. However, the patient developed dyspnoea and the injection had to be discontinued. Sulfadiazine, 0.125 gram every 6 hours by mouth was given for a period of six days. The swelling of the ankles disappeared gradually. The temperature declined by lysis and was normal for the last two weeks of the child's hospital stay. Blood culture after chemotherapy was sterile. The white cell count gradually came down to 9,300 (Feb. 8). Because the hemoglobin had dropped to 40 per cent (Jan. 30) the patient was transfused twice, with subsequent rise in hemoglobin to 74 per cent. The patient was discharged four weeks after admission in good general condition. The temperature was normal. The weight was 7 pounds 8 ounces. There was mild dyspnoea but no cyanosis.

The infant was later successfully operated on for his cataract by Dr. Reese and is now at the age of ten months in good general condition.

#### DISCUSSION

*a. The Congenital defects.* In recent articles published in Australian medical journals Gregg (2), Swan and his associates (3, 4) have pointed out that an attack of German measles in the mother during the early months of pregnancy may be followed by congenital defects in the subsequently born infant. The abnormalities encountered include cataract, heart disease, deaf mutism, microcephaly, obliteration of the bile ducts, equinovarus deformity, anomalies of the kidneys and mental deficiency. This observation was first made by Gregg, when in the early part of 1941 an unusual number of congenital cataracts appeared in Sydney following a severe epidemic of German measles in the summer of 1940. A subsequent investigation conducted by the above mentioned authors revealed that cases also occurred in many other parts of Australia during the year 1939 and 1943. The total number of cases recorded in Australia is 109. In most cases Rubella was contracted during the first three months of pregnancy. The number of cataracts following Rubella in the mother so far recorded in Australia

is 93, of which 20 cases were unilateral and 73 bilateral. In this country, of the three cases reported by Reese, two were bilateral and one unilateral. The reader is referred to Dr. Reese's paper for the details of the ophthalmological findings and for a more detailed summary of the Australian literature.

Congenital cardiac defects were present in 65 cases reported by the Australians. In this country the three cases published by Reese all had cardiac anomalies. Most of the cases seem to belong to the acyanotic group of congenital cardiac disease. A systolic or less frequently a systolic-diastolic murmur with the maximum intensity over the pulmonary area was heard in most cases. In some a thrill was present. In many, x-rays showed an enlarged and globular shaped heart. In the seven cases that came to autopsy a widely patent ductus arteriosus was found beside other minor lesions.

The latest report of this condition appeared in the October 1944 number of the *Journal of Pediatrics* by Carl A. Erickson who reported 11 infants with congenital cataracts whose mothers had suffered from Rubella within the first 3 months of pregnancy.

According to Gregg most of the infants are small sized, poorly nourished, difficult to feed and mentally retarded. Swan gives the average birth weight as 5 pounds 7 ounces. 15 of the 75 cases reported by Gregg died, several of bronchopneumonia. Our patient was of small size, a poor feeder and his gain in weight during the first few weeks of life was most inadequate. In this connection it is interesting to note how well the infant got over his severe meningococcus infection in spite of all of his handicaps.

*b. The Meningococcus infection.* In childhood, meningococcal infection in the great majority of cases takes the form of meningitis. However it is well known that there are conditions in which the meningococcus causes disease by attacking other organs than the meninges thus producing very dissimilar clinical pictures. In especially susceptible individuals or perhaps when the meningococci are particularly virulent, blood stream infection results in such overwhelming sepsis that death occurs before the meninges have a chance to become invaded. Such cases may take the form of the Waterhouse-Friderichsen syndrome. In other instances the disease is not so acute nor so virulent and a picture of a subacute febrile illness results which may drag on undiagnosed for a long time. In such cases the joints may become the foci of infection and mono-articular or polyarticular inflammation may result. The case described in this communication is remarkable for the following reasons: the disease occurred in very early infancy (7 weeks of age); it began as a fever of unknown origin, the joint involvement only appearing in the second week of illness; in spite of the fact that the patient was suffering from two severe congenital malformations, he made an excellent recovery without any apparent residual arthritic damage.

In the neonatal period multiple joint infections are well known, appearing as septic foci in so called sepsis of the newborn. Various organisms may be the etiologic agent, most common being the streptococcus, the staphylococcus, the gonococcus and the colon bacillus. We have had on our pediatric service a

child a few weeks of age with purulent arthritis of both shoulders, elbows, wrists, both hips, knees and ankles. This baby survived, only the two hip joints being permanently damaged, the other joints returning completely to normal.

Meningococcus arthritis is of particular interest because it may be part of meningeal disease or it may occur as an independent focus. Schein (5) in 1938 reported on 23 cases and thoroughly reviewed the whole subject. He divided the meningococcal arthritis as follows:

Type I. Meningococcal arthritis may be associated with epidemic meningitis.

(a) It may occur from a few days to as long as 2 months before the meningitis, in polyarticular fashion, resembling rheumatic fever, gonorrhoeal arthritis, etc.

(b) It may occur during the course of the meningitis.

(c) It may occur after the meningeal symptoms have disappeared, usually from the 4th to the 7th day.

Type II. Arthritis may occur with sepsis apart from meningitis.

Type III. It may occur as an isolated, localized infection with no other foci in the body.

Our case should be classified under Type II as there was no evidence of meningeal involvement and the blood culture was positive.

The frequency of arthritic complications in meningococcus disease is difficult to determine. Most of the statistics deal with groups of cases composed of both children and adults, and in almost all the cases the meninges are involved. Fox and Gilbert (6) reported 10 cases of arthritis among 266 meningococcus infections seen during the past 12 years. There were 4 cases in 215 patients before the era of chemotherapy (1.9 per cent) and 6 cases in the 51 patients treated in 2 years with chemotherapy (11.8 per cent). This increased percentage they ascribe to the survival of more severe cases. They quote the percentage incidence as found by other authors as follows: Rolleston 4.8 per cent; Councilman 5.4 per cent; Herrick 6.5 per cent; Bellevue Hospital series 7.7 per cent.

Of interest in this connection is a group of cases dealing with children only, recently reported from Chili by H. W. Jaeger (7). Within the space of 10 months 1,000 children suffering from meningococcus infections were treated in his hospital. In these arthritis was diagnosed clinically in 37 cases (3.7 per cent). However the author comments on the fact that in 52 cases which were examined at postmortem, 13 cases of purulent synovitis were discovered which had not been diagnosed clinically. Incidentally he also describes bursitis and tenosynovitis due to meningococci. His youngest case was aged 11 months. It had meningitis with purulent arthritis of one knee joint and recovered.

As we mentioned before, all these series deal with epidemic meningitis. Here and there in the literature an occasional case of meningococcal arthritis is reported in a very young infant not suffering from meningitis, but such cases are extremely rare.

Campbell and Greenfield (8) describe a previously healthy 15 months old in-



fant who developed fever and a swollen knee joint. There was no history of previous infection. Pus aspirated from the joint revealed meningococci. The outcome is not known.

Kobayashi (9) reports a 4 months old infant previously well who developed high fever and a morbilliform eruption. On the third day of illness there was involvement of the ankles, elbows, knees and wrist. Blood culture was sterile but fluid from the joints revealed meningococci. At no time were there meningitic symptoms. After an illness of 3 months, the baby recovered.

In 1921 French authors (10) recorded a fatal case in a 17 day old infant with arthritis of the knee and a cervical abscess secondary to an inflammation of the sterno-clavicular joint without meningitis.

The interesting question arises as to how these very young infants acquire their infection. In our case the infant was in an excellent obstetrical ward where infection with the meningococcus was most unlikely. He was then taken home where he was visited by the father and an uncle, both of whom were in the armed services and may well have been carriers due to sojourn in camps. The father's throat culture was negative for meningococci. The uncle's could not be obtained.

#### SUMMARY

An infant with congenital cataract and cardiac disease whose mother had Rubella during the first month of pregnancy is described. The relationship of the mother's illness to the child's defects is emphasized and the recent literature on this subject is briefly discussed. At 6 weeks of age the same infant developed meningococcus blood stream infection that localized in several large joints without meningitis. The infant was treated with sulfadiazine and anti-meningococcus serum and made an excellent recovery without any remnants of joint disturbance. The literature of meningococcus arthritis is very briefly summarized.

#### BIBLIOGRAPHY

- (1) REESE, ALGERNON B.: Congenital cataract and other anomalies following german measles in the mother. *Am. J. Ophth.*, 27: 483, 1944.
- (2) GREGG, N. M.: Congenital cataract following german measles in mother. *Tr. Ophth. Soc. Australia*, 3: 35, 1942.
- (3) SWAN, C., TOSTEVIN, A. L., MAYO, H., AND BLACK, G. H. BARHAM: Congenital defects in infants following infectious diseases during pregnancy, with special reference to the relationship between german measles and cataract, deaf-mutism, heart disease and microcephaly, and to the period of pregnancy in which the occurrence of rubella is followed by congenital abnormalities. *M. J. Australia*, 2: 201, 1943.
- (4) SWAN, C., TOSTEVIN, A. L., MAYO, H., AND BLACK, G. H. BARHAM: Further observations on congenital defects in infants following infectious diseases during pregnancy, with special reference to rubella. *M. J. Australia*, 2: 409, 1944.
- (5) SCHEIN, ALBERT J.: Articular manifestations of meningococci infections. *Arch. Int. Med.*, 62: 963, 1938.
- (6) FOX, M. J., AND GILBERT, JOS.: Meningococcus infections with articular complications. *Am. J. M. Sc.*, 208: 63, 1944.

- (7) JAEGER, H. W.: Meningocosis del aparato locomotor. *Rev. chilena de pediat.*, 14: 414, 1942.
- (8) CAMPBELL, W., AND GREENFIELD, E. C.: Meningococcal suppurative arthritis of cryptogenic origin. *South African M. J.*, 10: 545, 1936.
- (9) KOBAYASHI, MITSUGO: Ein Fall von Meningokokken Polyarthritis des Säuglings. *Orient. J. Dis. Infants*, 16: 22, 1934.
- (10) WEILL, DUFOURT AND BOCCA: Méningococcémie sans Méningite mais avec Arthrites purulentes multiples, chez un enfant de 17 jours, contagionné par sa mère. *Lyon méd.* 130: 504, 1921.
- (11) ERICKSON, CARL A.: Rubella early in pregnancy causing congenital malformations of eyes and heart. *J. Pediat.*, 25: 281, 1944.

## HYPERINSULINISM<sup>1</sup>

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The term hyperinsulinism was first employed by Seale Harris (1) in 1924 to describe a spontaneous syndrome indistinguishable from the hypoglycemic shock induced by an overdose of insulin. He hypothesized that the hypoglycemia with its attendant manifestations represented islet cell stimulation due to excessive food intake which might lead, in some instances, to insular exhaustion and diabetes. Nicholls (2) reported the first case of adenoma of the islands of Langerhans in 1902 and Warren (3) collected 20 cases of islet cell adenoma in 1926. In no instance was there clinical evidence of an associated hypoglycemic syndrome. Most of the reports, however, antedated the era of routine blood sugar determinations. In the following year Wilder and his associates (4) described the now classical example of carcinoma of the island of Langerhans with hepatic and lymphatic metastases associated with hyperinsulinism. Alcoholic extraction of a metastatic nodule in the liver, which bore a striking histologic resemblance to the cells of normal islet tissue, disclosed a high insulin assay and possessed the property of markedly lowering blood sugar concentrations when injected into rabbits. In 1929 the first reported instance of the postmortem finding of an islet cell adenoma in a patient with clinical hyperinsulinism appeared (5) and soon thereafter Howland and his associates (6) reported complete cure in a case of hyperinsulinism with coma and convulsions following the resection of an insular adenoma. Abundant reports of surgical cures in this condition soon followed.

Despite the growing recognition of this disease as a clinical entity, the term hyperinsulinism was often loosely applied to any form of hypoglycemia whether of hormonal, hepatogenic, central nervous or functional origin. In the absence of dependable criteria for differentiating insular from non-insular causes of hypoglycemia, exploration was usually confined to severe or fulminating cases or those which did not respond adequately to diet. As late as 1936 Harris (7) pleaded for the establishment of such criteria. This period of confusion was finally terminated with Whipple's (8, 9) now classical triad defining the bases for the accurate diagnosis of islet cell adenoma. These criteria are: A. An unusually low postabsorptive (fasting blood sugar level, 50 mg. per cent, or less). B. Symptomatic attacks of extreme hypoglycemia with signs of central nervous disorder, vasomotor or psychic, with, in some instances, coma or convulsions. C. Dramatic and immediate recovery following the administration of glucose orally or by vein.

With adherence to these criteria Whipple (10) found tumors of the islands of Langerhans in 19 or 22 cases in which operation was performed. Similar accuracy in diagnosis has been reported by many other observers. In a review of 105 cases of islet adenoma surgically removed, Whipple found only one patient with a fasting blood sugar level above 50 mg. per cent and this was 53 mg. It

<sup>1</sup> From the services of Drs. George Baehr and John H. Garlock.

is significant that in another clinic where these rigid criteria were not observed, tumors were found in only 16 of 46 cases.

At the Mayo Clinic (11) the surgical selection of cases differs in minor particulars from the Whipple standards. They are: a. normal health and evidence of stability of the autonomic nervous system prior to the first episode of hypoglycemia. b. postabsorptive blood sugar levels of less than 60 mg. per cent. c. intolerance to fasting. Although it cannot be gainsaid that most instances of endocrine and hepatic hypoglycemia are excluded by the first criterion, the stigmata, in varying degree, of emotional and autonomic instability are so general that the exclusion of such cases from operation is hazardous. The case to be reported presents an emphatic refutation of this somewhat arbitrary criterion. The choice of 60 mg. per cent as the uppermost level, although probably dependable in the great majority of cases, has not been found necessary in Whipple's much larger series. The "intolerance to fasting" which paraphrases Whipple's "postabsorptive state" is properly emphasized. In hyperinsulinism, hypoglycemic attacks often appear in from 12 to 20 hours following the ingestion of food and the "fasting test" in which food is withheld for as long as 30 hours will almost invariably precipitate an attack. A delayed breakfast, a skipped meal, anorexia, unusual physical exertion, menstruation or diarrhea may each provoke an episode. In the so-called functional, emotional and "nervous" hypoglycemias symptoms usually make their appearance in from 2 to 4 hours following meals and are frequently accentuated by a high or concentrated carbohydrate diet. During attacks the blood sugar level rarely falls below 70 mg. per cent. Prolonged fasts are, as a rule, well tolerated and postabsorptive blood sugar levels are not depressed.

Fraser and his associates (12) in an extensive metabolic study of a case of hyperinsulinism, found a continuous excess of an insulin-like substance as shown by the abnormal tendency of starvation or insulin to produce an hypoglycemic attack. They recommend an insulin tolerance test after 12 hours fasting thus obviating the need for prolonged starvation. Campbell and his co-workers (13) studied the insulin concentration in several islet cell tumors and found that it ranged from 4 to 40 times that of a normal pancreas per gram but did not exceed the insulin content of the entire organ. They conclude that the uncontrolled and erratic, rather than continuous, production of insulin in an islet adenoma is the probable cause of the hypoglycemic symptoms, especially in the early stages of the disease.

In hyperinsulinism the electroencephalogram, as recently emphasized by Wechsler and Garlock (14) presents a fairly characteristic pattern: short bursts of delta activity which become constant on hyperventilation. Following the administration of glucose the delta activity promptly disappears and the encephalogram becomes normal. These observers believe that the presence of an hypoglycemic pattern is a valuable diagnostic aid and that its persistence following resection of an islet cell adenoma indicates the presence of one or more residual functioning tumors. The encephalographic pattern of hyperinsulinism although indistinguishable from that of epilepsy, reverts promptly to normal following the ingestion of glucose.

The presence of wide and bizarre variations in sugar tolerance curves in hyperinsulinism has led to the belief that they are not of diagnostic importance. Whipple (15) and others (14, 16) however, describe a paradoxical or diabetic pattern in many cases. On the other hand, Conn (17) and later Duncan (18) insist that the assimilative curve *can* be of diagnostic value if performed under standard conditions. With the experience that a diet which has been either high or low in carbohydrate content preceding the test materially affects the glucose tolerance, these authors recommend 1. the avoidance of undernutrition and 2. the oral ingestion of 250 gms. of carbohydrate daily for 3 days preceding the test. Under these conditions the postabsorptive level in hyperinsulinism was found to be almost uniformly 50 mg. per cent or lower, the highest level thereafter rarely exceeding 120 mg. per cent, with a return to a subnormal level in 2 hours, where it is maintained for as much as 6 hours. This type of curve differs radically from those found in functional nervous disorders and infectious hepatitis. As an additional diagnostic feature Duncan (19) cites the extraordinarily rapid rate with which glucose was removed from the blood in the cases he studied.

#### PSYCHOSOMATIC ASPECTS

The nervous and emotional derangements frequently identified with hyperinsulinism have led to many erroneous diagnoses. In the period preceding the more general recognition of the disease, many cases were referred to neuro-psychiatrists, and Kepler and Moersch (20) collected 9 cases in which the early diagnoses included unexplained unconsciousness with or without convulsive features, acute confusional states, coma, alcoholism, brain tumor, hysteria, epilepsy and encephalitis.

Personality and behavior alterations of variable severity are frequently observed in the presence of an islet adenoma, and may run the whole gamut of psychologic symptomatology. Such phenomena have, to be sure, been noted in most hypoglycemic states, whatever the cause. Transient or prolonged periods of apathy, loss of zest, amnesia and fatigue may alternate with more acute attacks of tremulousness, weariness, vertigo and sweating. Wauchope (21) in 1933 described the protean manifestations of hypoglycemia in detail. He linked the symptomatology to disturbances at various cerebral levels and mentions such psychic disturbances as anxiety, negativism, irritability, querulousness, compulsions, etc. Romano and Coon (22) cite the case of a man with an islet adenoma who had recurrent attacks of confusion and bizarre behavior over a five year period which were interpreted as hysterical fugue states. During the hypoglycemic phase he showed uninhibited emotional behavior, incoherence, verbiage, negativism and disconnected movements. Previously inhibited aggressive and sadistic dreams were released periodically due to exhaustion of higher cerebral activity and a weakening of the ego structure. To quote Evans and McDonough (23) "hyperinsulinism has taken another syndrome from the waste basket of the neuroses." Alexander and Portis (24) in a psychosomatic study call attention to the profound inertia and relatively flat sugar tolerance

curves found in hypoglycemic fatigue. Himwich and his co-workers (25, 26) divide the psychological characteristics of hypoglycemia into 5 progressive phases and ascribe this sequence to variable metabolic rates throughout the brain. The cortical phase is indicated by sweating, muscular relaxation, salivation, tremors and gradual clouding of consciousness. In the second or subcortico-diencephalic phase, motor restlessness and primitive movements appear. The mesencephalic or third phase is characterized by tonic spasm and a positive Babinski frequently appears. A premyelencephalic phase follows with tonic episodes, chiefly extensor, simulating that of Sherrington's decerebrate dog. In the fifth or myelencephalic phase there is deep coma. These stages of hypoglycemic response have been best observed during the insulin treatment of schizophrenia.

#### PATHOLOGY

Islet cell tumors may be divided into two groups from a functional and clinical standpoint, those that produce the characteristic syndrome of hyperinsulinism and those that do not. At least one half of the recorded instances of islet adenoma have been chance findings at autopsy and clinically inert (27). They cannot, however, be distinguished histologically from functionally active tumors. Duff (27) finds the incidence of islet adenomas with hypoglycemia somewhat higher among males than among females and predominating between the ages of 20 and 40. Non-functioning insular adenomas are found chiefly in the later age periods. Although generally single, insular adenomas have been found to be multiple in 14 per cent of the reported cases. They are usually from 1 to 3 cm. in size but wide variations from microscopic tumors (at times indistinguishable from huge islet cells) to adenomas 15 cm. in diameter have been described. The severity of the hypoglycemia and attendant symptoms does not bear any proportional relationship to the size of the tumor; profound coma and convulsions have been reported in cases with a single minute adenoma. The tumors are, as a rule, discrete, sharply circumscribed and highly vascular. They present a purplish or reddish-gray color *in situ* and have a slightly firmer consistency than the surrounding pale yellow acinar tissue. Fibrosis, hyalinization and even calcification can occur. They are more commonly found in the tail of the organ. Tumors hidden deep in the substance of the head of the pancreas are not uncommon and present one of the more frequent causes of operative failure. Several instances of multiple adenoma requiring 2 or more explorations before a complete cure could be achieved have been reported (9).

The histologic arrangement of the islet cell adenoma consists of undulating and anastomosing ribbon-like strands of cells and closely resembles the morphology of normal or hyperplastic islands of Langerhans (fig.1). Some minor deviations have been recorded (27). The adenoma cells contain in varying proportion granules which stain like those of normal beta cells. Although beta cells have been held responsible for the elaboration of insulin (28) they have also been demonstrated in apparently inert adenomas (29).

Frantz (30) (table 1) in a series of comprehensive reviews of all the published



cases of hyperinsulinism to date, divides the tumors histologically into a. benign adenomata with well defined capsules, b. tumors with ill-defined capsules and questionable infiltration into the acinar tissue, c. malignant tumors with or without metastases, d. multiple microscopic and gross adenomatosis with, in some instances, infiltrative characteristics and e. a group of 11, somewhat ill-defined cases where in the pathologist's opinion there is merely hypertrophy and hyperplasia of the islets without neoplasia. Earlier observers were inclined to interpret the so-called hyperplastic group as analagous to the hypertrophic histologic picture seen in Graves' disease.

In another recent clinicopathologic study Frantz (31) describes several examples of *islet cell adenomatosis* associated with hyperinsulinism. The tumors

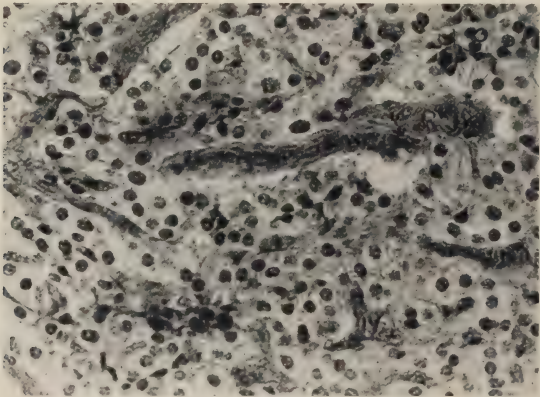


FIG. 1. Islet cell adenoma of pancreas

are small, usually multiple, at times numerous and are diffusely scattered throughout the pancreas. They are often characterized merely by hyperplasia and hypertrophy of islet tissue. It is probable that the 11 reported instances of "hyperinsulinism with functional hyperplasia of insular tissue" belong to this group. The extreme insular hyperplasia rarely observed in infants of diabetic mothers is presumably due to increased maternal demands. In most instances following a variable period of hypoglycemia the carbohydrate mechanism tends to revert to normal. Following partial pancreatectomy similar insular hyperplasia has been observed in the remaining pancreas.

Histologic differentiation between benign and malignant islet tumors is often difficult, sometimes impossible (31, 32). In Frantz' group (28), however, none of the 15 cases of so-called malignancy have shown any tendency to recurrence for periods of one to twelve years following resection. Other recent observers

share the impression that the morphologic picture of neoplasia or invasiveness is not clinically ominous and that the only true evidence of malignancy is the presence of metastasis. Frantz further states that in the group of questionable tumors "*the suspicion of the pathologist, not the surgeon, has yet to be confirmed in a single case by follow-up data.*" She also believes that in the multicentric cases, radical resection of the pancreas is indicated both because of the possibility of malignant disease and the danger of islet cell hyperplasia and neoplasia in the remaining pancreas with a return of hypoglycemia.

TABLE 1  
Summary of statistics  
(from Frantz)

|  | SINGLE | MULTIPLE | TOTAL | PER CENT<br>MULTIPLE |
|--|--------|----------|-------|----------------------|
| Tumors removed at operation and considered benign.           | 65     | 11       | 76    |                      |
| Tumors found at autopsy and considered benign. ....          | 26     | 4        | 30    |                      |
| Total benign tumors .....                                    | 91     | 15       | 106   | 14.2                 |
| Tumors removed at operation and suspected malignant.....     | 22     | 4        | 26    |                      |
| Tumors removed at autopsy and suspected malignant.....       | 2      | 0        | 2     |                      |
| Total suspicious tumors.....                                 | 24     | 4        | 28    | 14.3                 |
| Total cases of tumor <i>without proven malignancy</i> ... .. | 115    | 19       | 134   | 14.2                 |
| Carcinoma with metastases, <i>proven malignancy</i> .....    | 12     | 3        | 15    | 20.0                 |
| Total Cases of True Neoplasm.....                            | 127    | 22       | 149   | 14.8                 |
| Hypertrophy and hyperplasia without neoplasia.....           |        |          | 11    |                      |

Extrapaneatic islet cell adenomas have been described but they rarely produce symptoms. Bell and his associates (33) report a cure of hyperinsulinism following the removal of an islet tumor which was almost completely extrapaneatic, lying adjacent to the inferior border of the tail of the pancreas.

*Cerebral changes in hyperinsulinism:* The need for early recognition and prompt resection in cases of suspected insular adenoma is of especial importance in individuals where if operation is withheld, irreversible cerebral changes may occur. Kerwin (34) cites a case of abrupt onset with violent convulsions; coma ensued after 8 days despite the intravenous administration of glucose, with death 16 days after the onset of symptoms. Multiple pancreatic adenomas were found at necropsy with cerebral congestion, edema, hemorrhages, neural degeneration and gliosis. Malamud and Grosh (16) describe a case of islet adenoma with convulsions and psychotic manifestations which was correlated with advancing destruction of the cerebral cortex and basal ganglia. The diffuse degenera-

tive process in the brain was ascribed to the direct toxic effect of insulin on the parenchyma. Moersch and Kernohan (35) describe the pathologic changes in 2 cases; although some petechial hemorrhages in the pons were noted in one case, the most striking change in both instances was degeneration of the nerve cells. They stress the narrow margin between reparable and irreparable damage in both insulin induced shock and spontaneous hypoglycemia.

#### SURGICAL ASPECTS

In the exploration of islet cell tumors careful inspection and palpation of the adequately exposed tail, body and head of the pancreas is essential. Mobilization of the duodenum to the left will expose the posterior surface of the head. Whipple (9) found 3 tumors in this area in patients who had previously been unsuccessfully explored. The possibility of multiple tumors must always be borne in mind. If no adenoma is found, subtotal or total resection of the pancreas must be considered. David (36) collected 17 cases in the literature in which subtotal procedures were followed by favorable results and recommends removal of almost the entire pancreas (leaving only a small collar of the gland within the second portion of the duodenum) to insure a satisfactory result. This, it is hoped, would succeed in removing sufficient hypersecreting islet tissue as well as small adenomas otherwise overlooked.

Priestley and his co-workers (37) have recently described the first case of total pancreatectomy for an islet cell adenoma which was located only after serial section of the excised gland, deep in the substance of the head of the pancreas. The tumor measured 8 x 5 x 5 mm., one of the smallest on record. The surgical procedure was quite extensive and, because of the inadequate blood supply to the duodenum, a partial gastrectomy with removal of the first and second portions of the duodenum was required; a cholecystgastrostomy was done to establish internal biliary drainage. The patient is living and well 16 months after operation. The diabetes that supervened was surprisingly mild, requiring the daily use of only 16 units of insulin. No disturbance of carbohydrate digestion was detected but there was distinct diminution in the digestion of protein and fats. The unexpectedly small insulin requirement following total pancreatectomy has been further substantiated in 2 cases by Goldner and Clark (38). Blood sugar levels between 90 and 200 mg. per cent were maintained postoperatively with but minimal supplementary insulin. Both patients showed considerable insulin sensitivity, going promptly into hypoglycemia if the insulin taken was not adequately "covered" with carbohydrate. From the evidence of these 3 cases there is a strong likelihood that the insulin requirement of the depancreatized man is less than in many diabetics. This arouses speculation as to the existence of an insulin inhibiting mechanism, as well as a lack of insulin, in the causation of diabetes (39).

We have recently observed a case, reported by Umansky (40), with persistent hypoglycemia following subtotal resection of the pancreas. As the resected gland was found to be histologically normal, the existence of an islet cell adenoma in the small unresected portion of the head of the pancreas is presumptive. A total pancreatectomy will probably be required to effect permanent cure.

*Diet in hyperinsulinism:* Dietary control of hyperinsulinism is, at best, palliative and the symptomatic relief thus secured should not permit the postponement of operative cure. A high fat-high protein-low carbohydrate regimen with frequent feedings will in most instances prevent hypoglycemic attacks in the interval between diagnosis and operation. Prolonged dependence on the varied dietary regimens with which the literature abounds may induce a false sense of security and thus seriously compromise the outcome. There appears to be little virtue in other non-operative measures which have from time to time been recommended. These included the use of small doses of insulin, anterior pituitary, adrenal cortical hormone, thyroxin, Kendall's carbohydrate-stimulating factor E, epinephrin, ephedrin, bromides and the barbiturates.

Alloxan, the ureide of mesoxalic acid, has recently been employed in a case of carcinoma of the islet cells with multiple hepatic metastases (41). Based on the knowledge of its known necrotizing effect on the islands of Langerhans in the rabbit and dog, it was hoped that carcinomatous islet tissue in the human would be similarly destroyed. Temporary, and not clearly explained, relief followed its use in one case, but autopsy failed to disclose any necrosis in the malignant islet cells.

#### CASE REPORT

M. B., (Adm. #517713), aged 29 years, white married pianist had been in good health until July 29, 1943 when she retired at 11 p.m. and continued to sleep until 4:30 the following afternoon despite all efforts to awaken her. When finally aroused, she was bewildered and disoriented, perspiring profusely; her speech was thick and she complained of vertigo and diplopia. After eating breakfast, recovery was prompt. For the next three weeks, however, there was persistent drowsiness and she could rarely be awakened before 1 p.m. There were no convulsive seizures. Although conscious of the overpowering nature of the lethargy she found it impossible to arouse herself. Similar episodes would occur when a meal was inadvertently skipped. She soon learned the efficacy of sweetened drinks in preventing and controlling her symptoms and if awakened during the night to drink orange juice fortified with sugar, the morning attacks would be averted.

Her own description of her symptoms is of interest: "For several successive days I would be in a semiconscious state before arising. During these periods, which would last for 10 minutes to as much as 5 hours, I was told that I answered questions and would even eat breakfast without the slightest knowledge of having done so. At other times I was told that every possible attempt to awaken me would be futile, particularly if I clenched my teeth and refused food; the attacks would then last much longer. Shortly after eating I would become vaguely aware of my surroundings and on fully awakening would demand to know the date and hour. Early in my illness I would frequently awaken at night in a profound daze and find myself incapable of consecutive thought. I also found it impossible to organize my daily routine. I would fall asleep while reading letters, my fingers would fail to find the piano keys and I was unable to concentrate on reading. During the latter part of the day, although I never lost consciousness, I had frequent sensations of vagueness, listlessness, unreality and total exhaustion, sometimes associated with drenching perspiration which were relieved as soon as I took sweet or fatty foods; relief would then last for an hour or two when the "haze" would return. I was fully aware of my growing apathy, dullness and stupidity. Even when I was placed on a high fat diet with frequent meals these sensations, though milder and more transient, did not entirely disappear."

The clinical picture was at first interpreted as a profound psychasthenia which had been precipitated by separation from her parents, hard work and the prolonged, intense heat of the city of Washington, where she resided. She had been emotionally unstable,

introspective and easily frightened since early childhood; trivial annoyances would loom large and fresh situations precipitated intense anxiety. She had developed an obsessional fear of cats and would fly into a panic at the mere sight of one. A moderate hypochondriacal tendency had appeared in the last year.

She was admitted to the George Washington University Hospital in Washington, D. C. on August 23, 1943. Physical examination there was negative in every detail. On the regular hospital diet and bed rest she had no discomfort until August 27th, at 9 a.m. when she was found to be semicomatose and perspiring profusely. She was aroused with difficulty and resisted examination; her responses were sluggish and inaccurate; speech was slurred, her expression stupid and she was unable to focus adequately; her gait was staggering. The blood sugar level during the attack fell to 37 mg. per cent. On the following morning she had a similar episode with inability to speak, expressionless facies and involuntary movements of the right angle of the mouth. A "fasting test" was performed on August 30th and when breakfast was withheld until 9 a.m. she suddenly became dazed, was drenched in perspiration and unable to speak; within two minutes after the intravenous administration of 40 cc. of 50 per cent glucose she was fully alert, inquired the cause of the commotion and fell to eating her breakfast voraciously. On September 3rd she was found deeply comatose at 9 a.m.; there was marked twitching of the left corner of the mouth; the blood sugar level was found to be 10 mg. per cent. Response to intravenous dextrose was almost immediate. On the next day she automatically drank orange juice while in a semi-stupor with prompt response and no memory of the episode.

Laboratory investigations: Fasting blood sugar levels were successively 37, 28, 43, 36 and 45 mg. per cent. A sugar tolerance test with a fasting figure of 28 mg. showed, after the ingestion of 100 gm. of glucose, hourly figures of 36, 47, 52 and 59 mg. per cent thereafter. The hemoglobin was 95 per cent, the leukocytes numbered 10,150 and the differential count was normal. The spinal fluid was clear, under normal pressure, with adequate rise on jugular compression; total protein, 0.22 gm. per liter, globulin was absent. A skull roentgenogram was negative and the sella turcica normal. The urine was normal; specific gravity 1.019.

A high fat and protein diet with frequent feedings both day and night was instituted and the hypoglycemic episodes disappeared. At follow-up on November 30, 1943 the blood sugar level was 86 mg. per cent.

Although the major hypoglycemic episodes had been adequately controlled by the high fat-frequent feeding regimen, she complained of extreme fatigue, absent initiative, aimlessness, tremulousness, inability to concentrate and an oppressive sensation which she described as a "veil" over her head. The high fat diet had induced a degree of obesity which she felt was both cumbersome and unsightly. She was admitted for further study to The Mount Sinai Hospital on March 14, 1944.

*Examination:* The patient was listless and her responses were sluggish. The ocular fundi were negative. There was slight areolar hypertrichosis and the left breast was distinctly larger than the right. The systolic pressure was 134 mm. of mercury and the diastolic, 72. The muscular and neurologic status were negative. Despite her languor she was intelligent and cooperative.

*Course:* She was given the regular hospital diet and on the day following admission she was lethargic before breakfast but was perfectly well 20 minutes after eating; the fasting blood sugar level was 50 mg. per cent. On March 17th breakfast was delayed because of a gastrointestinal roentgen series and she had a seizure characterized by weakness, hunger and sweating. On March 21 food was purposely withheld for 18 hours and at 12:30 p.m. she became apprehensive, irritable and complained of vertigo and diplopia; articulation was clear and orientation good. The blood pressure was 150 mm. of mercury systolic and 100 diastolic. After drinking orange juice with sugar her symptoms vanished. On March 23 she experienced a very severe hypoglycemic attack at 5:30 a.m. with profound lethargy during which the blood sugar reached the level of 10 mg. per cent. The episode was followed by retrograde amnesia.



*Laboratory Data:* Fasting venous blood sugar figures were successively 50, 42, 50, 30, 10 and 34 mg. per cent. A sugar tolerance test with a fasting figure of 50 mg. per cent showed, following the oral ingestion of 100 gms. of glucose, 100, 200, 240, 240 mg. per cent at hourly intervals respectively; at the expiration of 4 hours there was 3.3 per cent sugar in the urine. Other tests disclosed: total blood protein, 7.9 mg. per cent; chlorides 1060 and sodium, 146.0 milliequivalents per liter; cephalin flocculation, 2 plus; icteric index, 6; lactose tolerance test, normal; hemoglobin 93 per cent, leukocytes 5,700; basal metabolism, minus 17 per cent. Gastrointestinal roentgenograms disclosed no abnormality; the gall bladder, however, did not visualize adequately; an electroencephalogram taken when the patient was fasting but not in hypoglycemic shock gave a normal record with bursts of 3 per cent activity following hyperventilation.

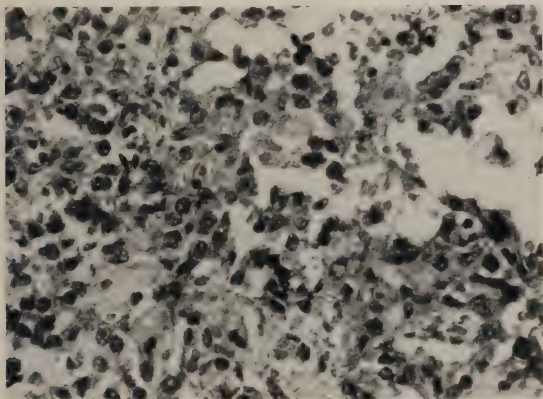


FIG. 2. Islet cell adenoma with hyaline changes

It was felt that the recurrent episodes of hypoglycemic shock associated with blood sugar levels of 10 to 50 mg. per cent appearing with some regularity from 12 to 18 hours following the ingestion of food indicated the presence of an islet cell adenoma with hyperinsulinism. Laboratory and clinical studies had excluded such causes of hypoglycemia as hepatic disease, organic disease of the nervous system, Addison's disease, myxedema and Simmond's disease. The possibility of a spontaneous hypoglycemia as a manifestation of her emotional instability was deemed hardly tenable. Exploration was therefore advised.

*Operation:* On March 29, 1944 a laparotomy (Dr. John H. Garlock) was performed under cyclopropane anesthesia after pre-operative preparation with 5 per cent intravenous glucose. Through an upper abdominal transverse incision the lesser sac was entered by cutting through the gastrocolic ligament. A careful exploration was made of the body and tail of the pancreas but no adenoma was found. This required mobilization of the organ from below upward. Most of the head of the pancreas was explored without result. With dissection of the second portion of the duodenum forward and to the left, it was possible to palpate the whole head between two fingers. After considerable dissection an adenoma was finally located in the uncinate process between the superior mesenteric vessels. The tumor was soft, reddish purple and measured 1.5 cm. in diameter. It was dissected



free from the pancreatic tissue and removed. Inasmuch as no other tumors were demonstrated the wound was closed after adequate internal hemostasis; following repair of the gastrocolic omentum a cigarette drain was placed in the lesser sac. The wound was closed in layers.

Histologic study of the removed specimen disclosed an adenoma of the islands of Langerhans with regressive hyalin changes (fig. 2).

There was an immediate post-operative diabetic reaction presumably identified with the use of intravenous glucose. The blood sugar levels reached 300 mg. per cent with a 3 per cent urinary sugar and a trace of acetone. The blood and urine soon returned to normal, insulin was not required and the patient had a fairly smooth convalescence. A mild infection of the original drainage tract responded promptly to chemotherapy. The fasting blood sugar levels varied from 75 to 100 mg. per cent until her discharge from the Hospital. A sugar tolerance test on April 24th disclosed a fasting blood sugar level of 75 mg. and 90, 105, 115 and 105 mg. per cent at 1, 2, 3, 4 and 5 hours respectively. On May 2 the fasting blood sugar level was 80 with 125, 135, 90 and 95 mg. per cent at 30 minutes, 1 hour, 2 hours and 3 hours thereafter. An electroencephalogram on April 25 disclosed a normal record. She was discharged on May 15, 1944 with an unrestricted diet and completely relieved of the hypoglycemic attacks. When last seen (February 15, 1945) she was alert, energetic and entirely free of any discomfort identified with her former illness. A sugar tolerance test was normal.

#### SUMMARY

A 29 year old woman suddenly experienced an episode of profound lethargy; recurrences were frequent. In the light of previous emotional instability and a rapid succession of psychic stresses, the clinical picture was at first interpreted as hysteria. With the finding of postabsorptive blood sugar levels as low as 10 mg. per cent and the occurrence of prompt relief from hypoglycemic attacks following the administration of glucose, the presence of hyperinsulinism due to an islet cell adenoma was presumptive. A high fat-high carbohydrate-frequent feeding regimen had succeeded in preventing attacks of lethargy and coma but did not completely eliminate the milder manifestations of hypoglycemia. After prolonged exploration, a small insular adenoma was removed from the uncinate process of the pancreas. Complete cure followed.

#### COMMENT AND CONCLUSIONS

When Whipple's diagnostic triad is met and pituitary, adrenal, thyroid, thalamic and hepatic disease have been ruled out, the presence of an islet cell adenoma is presumptive and operation should not be delayed. Such delay may permit the development of metastases and in some instances may result in irreparable cerebral damage with mental deterioration due to prolonged hypoglycemia. Operative results are almost uniformly spectacular.

Bizarre psychosomatic symptoms are frequently observed in hyperinsulinism. Personality and behavior disorders may be the sole manifestation of hypoglycemia and suggest the need for routine blood sugar determinations in all unexplained psychoneurotic and psychotic states.

As islet adenomas are frequently multiple, adequate exposure with careful inspection and palpation of the entire pancreas is necessary. Failure to find an adenoma justifies either subtotal or, as recently successfully performed,

*total* pancreatectomy. Most operative failures are due to an adenoma which has been overlooked deep in the substance of the head of the pancreas and not removed even after subtotal dissection. The persistence of hypoglycemic symptoms following either the removal of an adenoma or partial pancreatectomy indicates the need for secondary operation.

The existence of hyperinsulinism in the presence of hyperplastic and hyperfunctioning islet cells, without adenoma, is seriously questioned. Recent histologic studies would indicate that the hyperplastic zones actually represent multiple, frequently microscopic, adenomatosis.

The usual morphologic evidences of malignancy are not a valid index of malignancy in islet adenomas and the outlook for complete cure following resection of the tumor is excellent. The sole positive criterion of malignancy is the presence of metastasis, usually lymphatic or hepatic.

Glucose tolerance curves in hyperinsulinism are frequently ambiguous and have not proven to be of significant diagnostic import.

The symptomatic relief often obtained with high carbohydrate-high fat-frequent feeding regimens, lulls both physician and patient into a sense of false security and obscures the inexorable course of the disease with both an increase in the operative risk and lessening the chance for complete cure.

A case is reported.

#### REFERENCES

1. HARRIS, S.: Hyperinsulinism and Dysinsulinism. *J. A. M. A.*, 83: 729, 1924.
2. NICHOLLS, A. G.: Simple adenoma of the pancreas arising from an island of Langerhans. *J. M. Research*, 8: 385, 1902.
3. WARREN, S.: Adenomas of islands of Langerhans. *Am. J. Path.*, 2: 335, 1926.
4. WILDER, R. M., ALLAN, F. N., POWER, M. H., AND ROBERTSON, H. E.: Carcinoma of the islands of the pancreas, hyperinsulinism and hypoglycemia. *J. A. M. A.*, 89: 348, 1927.
5. McCLENAHAN, W. V., AND NORRIS, G. W.: Adenoma of the islands of Langerhans with associated hypoglycemia. *Am. J. M. Sc.*, 177: 93, 1929.
6. HOWLAND, G., CAMPBELL, W. R., MALTBY, E. J., AND ROBINSON, W. L.: Dysinsulinism, convulsions and coma due to islet cell tumor of the pancreas with operation and cure. *J. A. M. A.*, 93: 674, 1929.
7. HARRIS, S.: The diagnosis and treatment of hyperinsulinism. *Ann. Int. Med.*, 10: 515, 1936.
8. WHIPPLE, A. O., AND FRANTZ, V. K.: Adenoma of islet cells with hyperinsulinism. *Ann. Surg.*, 101: 1299, 1935.
9. WHIPPLE, A. O.: More recent developments in surgical therapy of islet cell tumors. *Proc. Inst. Med. Chicago*, 13: 63, 1940.
10. WHIPPLE, A. O.: Present day surgery of the pancreas. *New England J. Med.*, 226: 515, 1942.
11. WILDER, R. M.: *Clinical Diabetes Mellitus and Hyperinsulinism*. Philadelphia, W. B. Saunders Co., 1940, p. 358.
12. FRASER, R., MACLAY, W. S., AND MANN, S. A.: Hyperinsulinism due to a pancreatic islet adenoma. *Quart. J. Med.*, 25: 115, 1937.
13. CAMPBELL, W. R., GRAHAM, R. R., AND ROBINSON, W. L.: Islet cell tumors of the pancreas. *Am. J. M. Sc.*, 198: 445, 1939.
14. WECHSLER, I. S. AND GARLOCK, J. H.: Hypoglycemia and hyperinsulinism: With some remarks on electroencephalography. *J. Mt. Sinai Hosp.*, 10: 704, 1944.

15. WHIPPLE, A. O., AND BAUMAN, L.: Observations on the pathologic physiology of the insular and external secretory functions of the human pancreas. *Am. J. M. Sc.*, 201: 629, 1941.
16. MALAMUD, N., AND GROSH, L. L.: Hyperinsulinism and cerebral changes. *Arch. Int. Med.*, 61: 579, 1938.
17. CONN, J. W.: Spontaneous hypoglycemias: Importance of etiology in determining treatment. *J. A. M. A.*, 115: 1699, 1940.
18. DUNCAN, G. G.: *Diseases of Metabolism*. Philadelphia, W. B. Saunders Co., 1942, p. 659.
19. DUNCAN, G. G.: *Ibid.*, p. 660.
20. KEPLER, E. J., AND MOERSCH, F. P.: The psychiatric manifestations of hypoglycemia. *Am. J. Psychiat.*, n.s., 17: 89, 1937.
21. WAUCHOPE, G. M.: Hypoglycemia, a critical review. *Quart. J. Med.*, 26: 115, 1933.
22. ROMANO, J., AND COON, G. P.: Physiologic and psychologic studies in spontaneous hypoglycemia. *Psychosom. Med.*, 4: 283, 1942.
23. EVANS, J. A., AND McDONOUGH, W.: Hyperinsulinism. *J. Iowa M. Soc.*, 23: 454, 1933.
24. ALEXANDER, F., AND PORTIS, S. A.: A psychosomatic study of hypoglycaemic fatigue. *Psychosom. Med.*, 6: 191, 1944.
25. HIMWICH, H. E., BOWMAN, K. M., WORTIS, J., AND FAZEKAS, J. F.: Biochemical changes occurring in cerebral blood during insulin treatment of schizophrenia. *J. Nerv. & Ment. Dis.*, 89: 273, 1939.
26. HIMWICH, H. E., BOWMAN, K. M., DALY, C., FAZEKAS, J. F., WORTIS, J. AND GOLDFARB, W.: Changes in cerebral blood flow and arteriovenous oxygen difference during insulin hypoglycemia. *Proc. Soc. Exper. Biol. & Med.*, 45: 488, 1940.
27. DUFF, G. L.: The pathology of islet cell tumors of the pancreas. *Am. J. M. Sc.*, 203: 437, 1942.
28. LAIDLAW, G. F.: Nesidoblastoma, the islet tumor of the pancreas. *Am. J. Path.*, 14: 125, 1938.
29. WARREN, S.: Adenomas of islands of Langerhans. *Am. J. Path.*, 2: 335, 1926.
30. FRANTZ, V. K.: Tumors of islets of Langerhans with hyperinsulinism. *New York State J. Med.*, 41: 881, 1941.
31. FRANTZ, V. K.: Adenomatosis of islet cells, with hyperinsulinism. *Ann. Surg.*, 119: 824, 1944.
32. HANNO, H. A., AND BANKS, R. W.: Islet cell carcinoma of pancreas, with metastases. *Ann. Surg.*, 117: 437, 1943.
33. BELL, H. G., GOLDMAN, L., CRAIG, L. S., AND McCORKLE, H.: Hyperinsulinism. *Surgery*, 15: 681, 1944.
34. KERWIN, A. J.: Fatal hyperinsulinism with cerebral lesion due to pancreatic adenoma. *Am. J. M. Sc.*, 203: 363, 1942.
35. MOERSCH, F. P., AND KERNOHAN, J. W.: Hypoglycemia; neurological and neuropathologic studies. *Arch. Neurol. & Psychiat.*, 39: 242, 1938.
36. DAVID, V.: The indications and results of pancreatectomy in hypoglycemia. *Surgery*, 8: 212, 1940.
37. PRIESTLEY, J. T., COMFORT, M. W., AND RADCLIFFE, J.: Total pancreatectomy for hyperinsulinism due to islet cell adenoma. *Am. J. Surg.*, 119: 211, 1944.
38. GOLDNER, M. G., AND CLARK, D. E.: The insulin requirement of man after total pancreatectomy. *J. Clin. Endocrinol.*, 4: 194, 1944.
39. Editorial, *J. A. M. A.*, 125: 1193, 1944.
40. UMANSKY, A. L.: Subtotal pancreatectomy for hypoglycemia. *J. Mt. Sinai Hosp.*, 10: 698, 1944.
41. BRUNSCHWIG, A., ALLEN, J. G., OWENS, F. M., AND THORNTON, T. F.: Alloxan in the treatment of insulin producing islet cell carcinoma of the pancreas. *J. A. M. A.*, 124: 212, 1944.

## ARCUS SENILIS AND ARTERIOSCLEROSIS

ERNST P. BOAS

My interest in the arcus senilis was aroused by observing its occurrence in several young members of a number of families who were subject to familial xanthomatosis and hypercholesterinemia. This is not a new observation. Arning and Lippman (1) report the case of a 37 year old man with xanthomatosis and a marked arcus senilis. Joel (2) described several cases of arcus senilis in young people without manifest disease who all had high blood cholesterol figures. Among his cases were two brothers in their twenties. Klatskin (3) in a recent paper that gives a good review of the literature describes a family with xanthomatosis, many members of which also showed an arcus senilis. He suggests that both the xanthomatosis and the arcus senilis have the same underlying cause—a hypercholesterinemia.

The arcus senilis is a crescentic, opaque, white deposit in the cornea, occurring with increasing frequency with advancing years. It is caused by a deposit of refractile lipid globules, first in Bowman's membrane, later in Descemet's membrane and subsequently involving all layers of the cornea. This deposit consists largely of cholesterin. The arcus does not extend fully to the limbus, so that a clear band of cornea appears between it and the sclera. As its name implies, the arcus senilis has been regarded as one of the stigmata of aging, but in the past decades a number of authors have dissented from this view.

Versé (4) described the development of an arcus senilis in rabbits who were fed mixtures of cholesterin and oil. The authors quoted above point out the relationship in man between hypercholesterinemia and arcus senilis. Bürger and Schlomka (5), however, who noted an increase in the cholesterol content of the corneae of cattle with age, never observed hypercholesterinemia in persons with arcus senilis, not even in especially marked cases nor in those occurring in young people. They found no increased prevalence of arcus senilis in patients with diabetes or lipid nephrosis. Therefore they regard the cholesterin deposit in the cornea as a regressive process of senescence.

A number of authors have sought to relate the development of arcus senilis and atherosclerosis to the same pathogenetic process. Vollaro (6) described the frequent association of the two conditions, and observed this occurrence in a number of younger individuals. He ascribed both lesions to a fatty infiltration. Rohrschneider (7) found that although the simultaneous occurrence of arcus senilis and atherosclerosis is frequent, the relationship is not an invariable one. Because of the absence of hypercholesterinemia in most persons with arcus senilis or atherosclerosis, he concludes that the cholesterin deposits in the cornea and arteries are due to repeated transient rises in the blood cholesterin. This hypothesis is strengthened by the recent work of Steiner and Domanski (8) who determined the levels of serum cholesterin at intervals during periods up to two years, in a group of patients with coronary artery sclerosis, as well as in controls. They found for the coronary group figures ranging from 308 to 499

mgms. per cent, with an average of 355; for the controls levels ranging from 214 to 334 with an average of 255. The serum cholesterin levels in patients with coronary artery sclerosis are significantly higher than in the controls, and in those with coronary sclerosis the serum cholesterin level fluctuates widely from month to month, in contrast to the relative constancy of the serum cholesterin levels in the controls.

White (9) in a study of 400 autopsied cases found no relationship between the incidence of arcus senilis and arteriosclerosis. Scott (10) examined 2,891 patients with heart ailments for arcus senilis, and concluded that arcus senilis is more common in patients with arteriosclerotic heart disease. His data, however, are not presented convincingly.

TABLE 1  
*Frequency of arcus senilis*

| AGES  | TOTAL<br>NUMBER<br>OF CASES | MALE    |        |       | FEMALE  |        |       | PERCENTAGE OF<br>ARCUS SENILIS IN<br>EACH AGE GROUP |        |
|-------|-----------------------------|---------|--------|-------|---------|--------|-------|---|--------|
|       |                             | Present | Absent | Total | Present | Absent | Total | Male  | Female |
| 0-9   | 4                           |         | 2      | 2     | 0       | 2      | 2     | 0   | 0      |
| 10-19 | 21                          |         | 12     | 12    | 0       | 9      | 9     | 0   | 0      |
| 20-29 | 37                          | 1       | 17     | 18    | 0       | 19     | 19    | 5.5   | 0      |
| 30-39 | 66                          | 2       | 36     | 38    | 0       | 28     | 28    | 5.5   | 0      |
| 40-49 | 178                         | 10      | 89     | 99    | 3       | 76     | 79    | 10.0  | 4      |
| 50-59 | 463                         | 77      | 217    | 294   | 30      | 139    | 169   | 26.0  | 18     |
| 60-69 | 214                         | 55      | 94     | 149   | 20      | 45     | 65    | 37  | 30     |
| 70-79 | 17                          | 8       | 3      | 11    | 1       | 5      | 6     | 73  | 17     |
| Total | 1000                        | 153     | 469    | 623   | 54      | 324    | 377   | 24.6  | 14.3   |

I have examined 1000 consecutive patients in my office practice for the presence of arcus senilis. Most of these patients came for examination because of a real or supposed cardiac condition, so that the findings are not representative of the population at large. They were grouped according to diagnosis. Patients with a classical symptomatology of angina pectoris or cardiac infarction, or those with electrocardiographic alterations indicative of myocardial damage, and symptoms of coronary artery disease were classified as having coronary artery disease. If a patient had two conditions such as hypertension or diabetes and coronary disease, he was placed in the category of coronary artery disease.

Table I presents a survey of the whole 1000 cases. It is evident that the clinical arcus senilis develops at an earlier age in males, beginning in the third decade, and that after the age of 50 there is a rapid increase in its incidence. In women below the age of 50 it is unusual to encounter arcus senilis, but after this age its frequency rapidly increases but does not approach the frequency that is encountered in males.

The distribution of arcus senilis between the sexes and the several age groups approximates the incidence of arteriosclerosis. It seemed worth while, there-



fore, to classify the material in an attempt to discover whether arteriosclerosis, as measured by the presence of coronary artery disease, was more frequent among persons with arcus senilis, than among those who do not have this corneal deposit. Since both arteriosclerosis and arcus senilis become increasingly frequent with advancing years it is profitable to compare only patients of the same age groups. This analysis is presented in Table II. The behavior of males and females appears to be different. In males with arcus senilis the incidence of coronary disease is appreciably higher in each age group up to age 70 than among those without arcus senilis. Among females the frequency of coronary disease also appears to be higher among those with arcus senilis, except in the age group 40-49. In this group 12 per cent of those without arcus senilis have

TABLE II

*Frequency of coronary artery disease in the absence or presence of arcus senilis*

| AGES    | PERSONS WITHOUT ARCUS SENILIS |                       |          | PERSONS WITH ARCUS SENILIS |                       |          |
|---------|-------------------------------|-----------------------|----------|----------------------------|-----------------------|----------|
|         | Total number                  | With coronary disease |          | Total number               | With coronary disease |          |
|         |                               | Number                | Per cent |                            | Number                | Per cent |
| Males   |                               |                       |          |                            |                       |          |
| 30-39   | 36                            | 10                    | 27.7     | 2                          | 1                     | 50.0     |
| 40-49   | 89                            | 48                    | 53.9     | 10                         | 8                     | 80.0     |
| 50-59   | 217                           | 140                   | 64.5     | 77                         | 59                    | 76.6     |
| 60-69   | 94                            | 69                    | 73.4     | 55                         | 42                    | 76.3     |
| 70-79   | 3                             | 2                     | 66.6     | 8                          | 4                     | 50.0     |
| Females |                               |                       |          |                            |                       |          |
| 30-39   | 28                            | 0                     | 0        | 0                          | 0                     | 0        |
| 40-49   | 76                            | 10                    | 12.1     | 3                          | 0                     | 0        |
| 50-59   | 139                           | 45                    | 32.4     | 30                         | 11                    | 36.6     |
| 60-69   | 45                            | 23                    | 51.1     | 20                         | 15                    | 75.0     |
| 70-79   | 5                             | 2                     | 40.0     | 1                          | 1                     | 100.0    |

coronary disease, whereas none of the 3 with arcus senilis have such evidence of arteriosclerosis.

A different classification of cases is found in Table III where the frequency of arcus senilis in the presence or absence of coronary disease is presented. Here we again find a higher incidence of arcus senilis in patients with coronary artery sclerosis.

It is not suggested that the relationship between arcus senilis and arteriosclerosis is an absolute one, that the two always occur concomitantly. Factors other than cholesterol are certainly concerned in the genesis of arteriosclerosis. But the data here presented suggest that the frequent association of the arcus senilis with arteriosclerosis is more than accidental.

Further support for this view is found in the simultaneous occurrence of these two conditions in patients with hereditary xanthomatosis or familial hypercho-



lesterinemia. With Dr. Adlersberg (11) I have been studying a number of families exhibiting this syndrome and we have encountered not a few younger persons who with hypercholesterinemia and arteriosclerosis also had well marked development of the arcus senilis.

In addition I have under observation a number of patients under the age of 40 who do not belong to xanthoma families who have clear cut coronary artery disease, a well marked arcus senilis, and an elevation of the cholesterin in the blood.

TABLE III

*Frequency of arcus senilis in the presence or absence of coronary artery disease*

| AGES    | PERSONS WITH CORONARY DISEASE |                    |          | PERSONS WITHOUT CORONARY DISEASE |                    |          |
|---------|-------------------------------|--------------------|----------|----------------------------------|--------------------|----------|
|         | Total number                  | With arcus senilis |          | Total number                     | With arcus senilis |          |
|         |                               | Number             | Per cent |                                  | Number             | Per cent |
| Males   |                               |                    |          |                                  |                    |          |
| 30-39   | 11                            | 1                  | 9        | 27                               | 1                  | 3.7      |
| 40-49   | 55                            | 8                  | 14.5     | 43                               | 2                  | 4.6      |
| 50-59   | 199                           | 59                 | 29.6     | 95                               | 18                 | 19.0     |
| 60-69   | 111                           | 42                 | 37.8     | 38                               | 13                 | 34.2     |
| 70-79   | 6                             | 4                  | 66.6     | 5                                | 4                  | 80.0     |
| Females |                               |                    |          |                                  |                    |          |
| 30-39   | 0                             | 0                  | 0        | 28                               | 0                  | 0        |
| 40-49   | 12                            | 0                  | 0        | 69                               | 3                  | 4.4      |
| 50-59   | 55                            | 11                 | 20       | 113                              | 19                 | 16.8     |
| 60-69   | 48                            | 15                 | 31.2     | 27                               | 5                  | 18.5     |
| 70-79   | 3                             | 1                  | 33.3     | 3                                | 0                  | 0        |

## SUMMARY

The association of arcus senilis and coronary artery sclerosis was studied in a series of 1000 consecutive patients seen in office practice. There appears to be a definite correlation in the appearance of these two phenomena. A similar association has been noted in patients with familial xanthomatosis and hypercholesterinemia, as well as in a number of young patients with coronary artery disease and hypercholesterinemia. These findings suggest that a disturbance of cholesterin metabolism is concerned in the genesis of at least some cases of arteriosclerosis.

## BIBLIOGRAPHY

1. ARNING, E., AND LIPPMANN, A.: Essentielle Cholesterinämie mit Xanthombildung. *Ztschr. f. klin. Med.*, 89: 107, 1920.
2. JOEL, E.: Der Arcus Corneae bei Jugendlichen. *Klin. Wehnschr.*, 3: 269, 1924.
3. KLATSKIN, G.: Familial Xanthomatosis and Arcus Senilis. *Internat. Clin.*, 3: 13, 1941.
4. VERSÉ, M.: Ueber d. Blut u. Augen Veränderungen bei exp. Cholesterinämie. *München med. Wehnschr.*, 63: 1074, 1916.

5. BÜRGER, M., AND SCHLOMKA, J.: Beitr. z. physiol. Chemie d. Alterns. d. Gewebe. Ztschr. f. d. ges. exper. Med., 61: 465, 1928.
6. VOLLARO: Della "steatosi" oculare senile e del suo nesso patogenetico con le alterazioni "atherosclerotiche" senile delle arterie. Arch. di ottal., 18: 345, 1910.
7. ROHRSCHEIDER, W.: Ueber d. Arcus lipoides corneae senilis, seine Entstehung u. seine Beziehungen z. Verfettungszuständen anderer Organe insb. z. Atherosklerose. Klin. Monatsbl. f. Augenh., 74: 93, 1925.
8. STEINER, A., AND DOMANSKI, B.: Serum cholesterol level in coronary arteriosclerosis. Arch. Int. Med., 71: 397, 1943.
9. WHITE, C. E.: The relation of arcus senilis to arteriosclerosis and senility. New England J. Med., 212: 10, 1935.
10. SCOTT, C. L.: Arcus senilis an accompaniment of cardiovascular disease. South. M. J., 241: 165, 1931.
11. ADLERSBERG, D., AND BOAS, E. P.: Familial Hypercholesterinemia (Xanthomatosis) and Arteriosclerotic Cardiovascular Disease. Read before the New York Heart Assoc., May 2, 1944.

## FAMILIAL HYPERCHOLESTEROLEMIA (XANTHOMATOSIS) AND ATHEROSCLEROSIS<sup>1</sup>

ERNST P. BOAS, M.D., AND DAVID ADLERSBERG, M.D.

[From the Medical Service of Dr. George Bachr, The Mount Sinai Hospital, New York, N. Y.]

The association of xanthomatosis, hypercholesterolemia and cardiovascular disease, as well as the familial occurrence of this syndrome is well established (Müller, Thanhauser, Bloom and others). The purpose of this communication is to call attention to the relative frequency of this condition, to its importance as a cause of sudden death, and to its relationship to atherosclerosis. Within 6 months we encountered 7 families in whom this disease was prevalent. One family was of Irish descent, one of Armenian and 5 were Jewish. We have examined 55 members of these families. In the same period of time we have seen 9 additional individual cases, whose families we were unable to study.

Of these 64 individuals only 18 exhibited the full syndrome, i.e., skin lesions, coronary artery disease and hypercholesterolemia. The manifest lesions, namely xanthelasma, xanthoma tuberosum of the skin, or xanthoma tendinosum, arcus senilis, atherosclerosis of the coronary or other arteries, and elevation of the blood cholesterol are found in varied combinations. Of our 64 cases, 20 presented xanthelasmas, 13 xanthoma tendinosum or tuberosum, 10 arcus senilis, and 24 had evidence of coronary or peripheral atherosclerosis. The most constant feature is the elevation of the blood cholesterol. Using 250 mg. per cent as the upper limit of normal, 50 cases had high blood cholesterol figures (most of them over 350 mg. per cent). In many individuals the only manifestation of the disorder is a high level of blood cholesterol. We encountered this in many children and young adults belonging to these families. Of 15 cases in which the blood was examined for uric acid, 7 had figures above 6 mg. per cent. They ranged from 6.1 to 9.0 mg. per cent. In none of these cases was there evidence of gout or of kidney insufficiency.

The hereditary nature of this disorder is evident from the study of the family trees and of the literature. Our analysis confirms the view that the hereditary element is a disturbance of the lipid metabolism, manifesting itself in hypercholesterolemia. The development of skin manifestations, arcus senilis and vascular lesions depends on additional factors which are still obscure. Marriage of two individuals both showing the disorder intensifies the disease manifestations in their offspring, while the marriage of an abnormal to a normal individual dilutes the predisposition to the development of the manifest disease. The offspring of such marriages tend to show only hypercholesterolemia, although the parent may exhibit the fully developed syndrome. Members of families with hypercholesterolemia who present only an elevated blood cholesterol should be regarded as carriers of the familial predisposition and as having the disease in its preclinical stage.

<sup>1</sup> Presented at a meeting of the N. Y. Heart Association, May 2, 1944.

In one of our families 3 siblings died suddenly of coronary artery disease at the ages of 31, 37 and 43 (fig. 1). This family first came to our attention through Mrs. B. when she experienced a coronary thrombosis. At this time she exhibited xanthelasmas of the eyelids and a blood cholesterol of 525 mg. per cent. She died suddenly a few months later, at the age of 43, probably from another coronary occlusion. Two brothers and one sister of Mrs. B. had blood cholesterol figures of 400, 410 and 560, respectively. One brother had xanthoma tuberosum, the other had coronary artery disease. Two other brothers had died at the ages of 37 and 31 respectively of coronary artery disease. We were able to find the hospital record of the younger brother. His autopsy revealed advanced

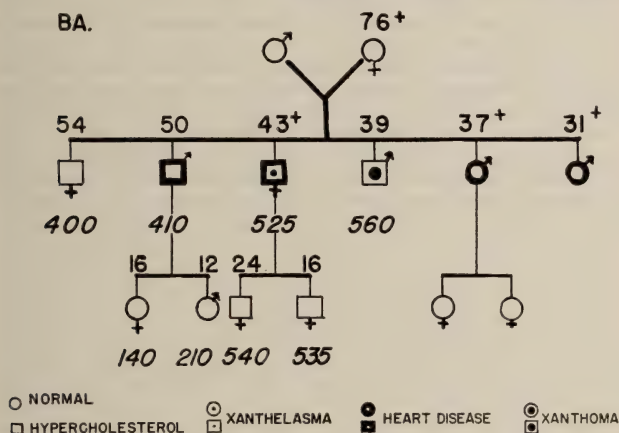


FIG. 1

arteriosclerotic cardiovascular disease. The two children of Mrs. B., aged 24 and 16, had blood cholesterol levels of 540 and 535 mg. per cent respectively, without any manifestations of the disease. The two children of her older brother, aged 16 and 12, had normal cholesterol figures. At the time the 31 year old brother died, his blood cholesterol was not studied and it was unknown that he belonged to a hypercholesterolemic family. At post mortem he was regarded as a case of far advanced arteriosclerosis of unknown origin in a young man. It was only 15 years later when his sister, Mrs. B., came under observation and the family was studied that the true nature of the disorder became apparent. Such situations must be common. Careful studies of patients with coronary disease will undoubtedly unmask many such instances of familial hypercholesterolemia.

There does not appear to be any direct connection between hypertension and the syndrome under discussion. Our observations suggest that when a person

with familial hypercholesterolemia has hypertension as well, this accelerates the development of his arterial disease.

Most authors still distinguish between xanthomatous deposits in the arteries and atherosclerosis. The studies of Aschoff, Anitschkow, Leary, and others have demonstrated that the earliest lesions of atherosclerosis are represented by lipid infiltrations of the intima and the development of foam cells in the subendothelial layer of the arterial intima, lesions which are indistinguishable from those found in xanthomatosis. Similar lesions are found in experimental cholesterol atherosclerosis in rabbits. Hirsch and Weinhouse conclude from their extensive studies that atherosclerosis develops from disturbances in metabolism of lipids, infiltrated into the tissues of the intima. The frequency of atherosclerotic heart disease in familial hypercholesterolemia, and particularly its occurrence in young individuals gives support to this theory. Although xanthomatous nodules occur rarely in the large vessels and on the heart valves, in many cases the arterial lesions in xanthomatosis are indistinguishable from those of ordinary atherosclerosis. Further studies of familial hypercholesterolemia promise to contribute to our knowledge of the causes of atherosclerosis.

These studies have a practical importance, as well. All members of families with familial hypercholesterolemia, as potential candidates for atherosclerotic cardiovascular disease, should be kept under permanent medical supervision.

## TWENTY-FIVE YEARS OF PHYSIOLOGICAL CHEMISTRY AT THE MOUNT SINAI HOSPITAL (1902-1927)

SAMUEL BOOKMAN, PH.D.<sup>1</sup>

The Nineteenth Century was a period devoted, among other great technical advances, to the formation and development of the science of physiological chemistry. During the beginning of this present century, in its first three decades, the matured science saw its extensive application to the problems of clinical medicine, to the development of tests for visceral functions.

The change of the century really marked the beginning of the organization of biological and physiological chemistry in laboratories established for such purposes.

My own education at Columbia University, School of Mines, was followed by a typical course in post-graduate studies at the University of Berlin. Such topics, characteristic of the times, included the subjects of biology, bacteriology, physiology, clinical physiological and pathological chemistry to round out the essential fundamentals.

The Pathological Institute of the New York State Hospital under the direction of Dr. Ira Van Gieson was noted for its alert interest in the problems of the day, so that my appointment as "Associate in Physiological Chemistry" seemed a recognition of the thoroughness and modernity of the post-graduate erudition of the Germany of that day.

The names of the staff of that institution, young men in their earlier years, without exception made scientific history as their lives matured. The roster is inspiring: it includes Dr. P. A. Levene, Associate in Physiological Chemistry; Dr. Harlow Brooks, Bacteriology, Dr. Arnold Graf, Associate in Biology, Dr. H. B. Deady, Pathology, Dr. Boris Sides, Associate in Psychology, Dr. Alex Hrdlicka, Associate in Anthropology, Dr. C. J. Herrick, Associate in Comparative Neurology.

There were in addition many volunteers in the Service amongst whom were Dr. Richard Weil, later an Adjunct Visiting Physician at Mount Sinai, and also my brother, Dr. Arthur Bookman.

Much of the stimulus for the interest in Physiological Chemistry emanated from the personality of Dr. Russell H. Chittenden. While occupying the Chair at Yale University, he visited and gave a course at the College of Physicians and Surgeons (1898). A nucleus of enthusiastic scientists formed themselves into a group to carry on the investigations into this science and its related fields. A small informal society was created, including in its personnel such outstanding names as Doctors James Ewing, Graham Lusk, John Mandel, Phoebius A. Levene, William J. Gies, Alfred N. Richards, P. B. Hawk, Virgil Coblentz, W. N. Berg, William Salant, and later George B. Wallace and many others.

The central laboratory of the Pathological Institute of the New York State

<sup>1</sup> This paper is dedicated to the many co-workers who during these years, and often at great personal sacrifice, gave their time, energy and effort to help build up this Department.



Hospitals acted as a technical and training center. During my own tenure of office, the methods of modern science were introduced into the recently established laboratories of the State Hospital system just completed at Utica, Ogdensburg, Poughkeepsie, Buffalo, Binghampton, and Ward's Island, N. Y. C.

In The Mount Sinai Hospital the first signs of interest in the subject of Physiological and Pathological Chemistry were just beginning to become apparent. Dr. Julius Rudisch had designated a small corner in the Clinical Laboratory on the first floor of the South Wing with one window on 66th St. Such limited space did not promise opportunity for extensive research or routine. The actual establishment of such a department took place in 1904 with the erection of the new hospital buildings on 100th Street. This was probably the first voluntary hospital in New York City to have established a separate department in Physiological Chemistry.

The planning of these buildings to house the Pathological Laboratories had been assigned to and accepted with pleasure by Dr. Fred S. Mandlebaum. In consort with him, we planned the details of constructing and equipping the projected laboratories. The architects' plans required many changes, such as would be familiar only to one who had lived and worked in laboratories for years. Thus in the original plans for the Chemical Laboratory the window sills had been advertently sketched as eight inches higher than the tops of the laboratory desks. To lower the window sills to the proper level would affect the architectural symmetry of the north facade on 101st Street.

The unofficial status of "Adviser" to the planning of the hospital was on February 1, 1902, converted by my actual appointment, to that of "Associate in Physiological Chemistry"; with the dedication of the new site and buildings the Department was inaugurated as a working unit. This condition still prevails.

The first volunteer research assistant in the Department was no other than Dr. Julius Rudisch who at that same time was the Visiting Physician to the First Medical Service. Dr. Rudisch could be seen many an afternoon after completing Ward Rounds, puttering around the Chemical Laboratory, interested in uric acid in the blood, quantitative acetone in the diabetic urine, and many similar subjects. Many of the men who later played prominent rôles in the hospital began their career in the laboratories devoted to Biological Chemistry. The first of these was Dr. Edward A. Aronson (later the first Gastroenterologist) followed soon by Doctors Arthur Bookman and A. A. Epstein, the latter in charge of research. In the course of twenty-five years, over fifty assistants served in the department, men busy or about to be busy in practice, part-time non-salaried men, who by enthusiasm and expertness of skill and in a spirit of friendly cooperation, managed not only the routine of the large and growing hospital but succeeded annually in publishing meritorious research studies.

Among these colleagues and volunteer assistants were included such names as: Louis Hauswirth, Burrill B. Crohn, Theodore Kuttner, Joseph Reiss, Marcus A. Rothschild, Jerome L. Kohn, Herman Schwarz, Hubert Mann, Lewis Mann, Joseph Harkavy, Selian Hebal, Margaret Fries, Mrs. Maechlin, Herman Lande, Irving Gray, Joseph Marcus, Daniel Poll, Nathan Rosenthal, Joseph Felsen,

Moses Zwick, Samuel Rosen, Saul S. Samuels and the late Philip Finkel. This roster from memory, may not be complete; as the work and scope of the department developed, additional assistants to the department, joined the staff. The work was at all times conscientiously performed, always in close cooperation with the clinical branches, so bridging the space between the pure and the applied sciences and clinical routine and research.

The quality of the routine work accomplished by this department is reflected in the perusal of the daily charts of most of the patients in the wards of the hospital.

Its record for scientific research is manifest in the voluminous publications originating in this department during the past forty years. Among notable contributions was that of Epstein on Nephrosis and the High Protein Diet, Rothschild's work on the cholesterol content of the blood in gall bladder disease; that of Crohn on early fractional estimations of gastric contents, its diagnostic values as well as pioneer studies on pancreatic metabolism and quantitative ferment analysis. Kuttner's work in micro-chemical and colorimetric methods was fundamental and extremely ingenious. Dr. S. Bookman was interested in the chemical analysis of kidney calculi and gall stones, their composition and structure. This brief, very brief mention does scant justice to the research work and publications of the many unselfish members of the volunteer staff.

Visitors to the Department were not unusual. Dr. Nathan E. Brill loved to delve into matters chemical; such notable persons as Dr. William Osler, Dr. William H. Welch, Dr. Chaim Weitzmann, Dr. Albert Einstein, Dr. Arbuthnot Lane were among other prominent physicians and scientists who graced the confines of the laboratory.

#### THE GROWTH AND DEVELOPMENT OF THE DEPARTMENT

1. *Structural.* The original laboratory building stood within the courtyard facing on 101st St., it was opened in 1904 and was continued there until 1922 when the main laboratory building on 99th St. was inaugurated and occupied by the enlarged staff. The old building has been partially rebuilt and is now occupied by the laboratories for serology, for cancer research and for neurological anatomy and pathology.

2. *Personnel.* The original staff of this laboratory consisted only of a Physiological Chemist and his volunteer associates. Between 1904 and 1927 this staff was constantly augmented as chemistry came to play a larger and more vital rôle in diagnosis and in visceral functional tests. In 1927 at the end of the period of part-time workers, the staff included nine associates and assistants, all volunteers, all practicing physicians, devoting from a few hours to six hours daily to their respective tasks. There was only one salaried full-time worker. The tenure of office of the associates and assistants varied from a term of one year to as many as fifteen years in some cases.

3. *Scope of work.* The first year there were only a few hundred routine examinations. In the last year of my tenure of office, 1927, about nine thousand routine examinations were performed by the staff. In addition, each assistant

was engaged in some research work connected with his branch of medicine or in the origination or improvement of methods in clinical chemistry or in chemical pathology. The departments represented by the staff of associates and assistants were those of general medicine, gastro-intestinal diseases, otology, allergy, surgery and other branches.

As the work increased from year to year, it became more difficult to conduct it on the old basis. Its growth and development demanded a staff of a salaried chief and salaried assistants which was the natural trend of all laboratories in this as well as in other hospitals. The close cooperation and cordial relationship of the laboratory to the members of the medical and lay boards of the hospital have always been an incentive to the work performed in the laboratories.

[In 1927 my resignation as Physiological Chemist was accepted. Dr. Michael Heidelberger, succeeded me; his short tenure of the position was followed by his appointment as Associate Professor of Physiological Chemistry at the College of Physicians and Surgeons of Columbia University. His subsequent work in the field of immunology has been outstanding. In 1928, Dr. Harry Sobotka became Chemist to the Hospital and his able and efficient department, as well as his splendid and outstanding work in many fields is universally recognized.

In 1927 Dr. Bookman was appointed "Consulting Chemist" to the hospital an honor which was well deserved and merited. He has always continued to manifest an interest not only in the laboratories but also in the teaching and clinical branches of the hospital. On his resignation, Dr. Bookman received from the Board of Trustees of the Hospital the following letter:

"On behalf of my colleagues, I desire to tender you our sincere thanks and gratitude for your long years of faithful service. You began the development of your Department when chemistry established its first relation with clinical medicine and at times must have labored under conditions which were very trying. In spite of many handicaps you continued with patient perseverance, with the result that your Department developed successfully and to the point where you may well look back with pride upon the effects of your work. The example of conscientious endeavor which you have always set for the younger men has been particularly commendable."—B. B. C.]

We all have great hopes that the new laboratory buildings for the hospital projected in the near future, will be another step forward in the firmer establishment of scientific medicine as an aid to the amelioration of human suffering, in the treatment of disease and in the education and training of the practicing physician in modern and improved methods of scientific research.

## THE MODIFIED INSULIN TECHNIQUE IN THE TREATMENT OF AMBULANT PSYCHIATRIC PATIENTS

RICHARD M. BRICKNER, M.D.

In an attempt to discover whether a state of coma was essential to success in the insulin treatment of psychotic patients, Polatin, Spotnitz and Wiesel modified Sakel's original method. They gave the insulin by vein or subcutaneously (1, 2). By their method, with the avoidance of coma, the patient can take sugar-containing solutions voluntarily, and the whole procedure is simpler and safer than the coma-producing procedure. The results are said to compare favorably with those obtained by the Sakel technique.

Since the report of these authors in 1940, a number of other communications on the subject have appeared. The attention of workers has been attracted to the method for various reasons—in England, MacGregor and Sandison used insulin intravenously to save insulin under war-time conditions (3); Tomlinson and Ozarin employed it subcutaneously because it could be given with a minimum extra staff at the hospital and at small expense (4).

That insulin could be of help to patients with mental and emotional disorders was actually known long before its use became systematized and practical. This would necessarily be so, once insulin began to be used in the treatment of any large group of human beings. It is of interest to see, for example, that Cowie, Parsons and Raphael observed in 1923, the "remarkable clearing of the depression in diabetes with insulin treatment" (5). Other occasional observations of like significance appear in the literature. In 1929, Appel, Farr and Marshall gave insulin to improve the nutrition of psychotic patients and obtained striking improvement in the mental states of some of their cases (6). According to the latter authors, Targowla and Lamanche had already reported similar results in 2 undernourished cases of psychosis and Miskolczy, again seeking to improve nutrition, had also noted a beneficial effect in a small series. Bennett and Miller writing in 1940, enthusiastically described the use of small subcutaneous doses of insulin in quieting disturbed state hospital patients (7). They spoke of "miraculous improvement" in early manic-depressive, other depressive and schizoid states. They, like other authors, pointed out that treatment must be continued for 3 to 8 weeks, if sustained improvement is to be expected. Polatin and Spotnitz treated one schizophrenic of very long standing for  $2\frac{1}{2}$  years, and another for over 1 year (8).

Rennie has recently reported a series of 28 psychotic patients, who received insulin subcutaneously, without the production of coma; he observed marked improvement in 19 and some improvement in 4 more cases. Rennie's interpretation was that anxiety was the essential factor which was relieved (9).

This brief summation from the literature is not intended as a review, but an indication of what has been done. Ample reviews can be found in the papers of Polatin and his co-workers. They are to be credited with having worked out a

simple method which is of immense help in the treatment of many different sorts of mental and emotional disturbances.

The present paper describes the results obtained by the use of the ambulant method in 18 cases. Eleven were treated over fairly long periods and seven occasionally. The patients were not as sick as those of other authors, because all the previous series have emanated from hospitals; the present group was ambulant. Nonetheless, some mildly psychotic patients are in the group.

Treatment over reasonably long periods was administered by the following technique:

1. *Time*: The injections were given in the morning to the fasting patient, who had brought with him the juice of two oranges.

2. *Garb*: The patient's clothing was replaced by a gown (important because of the extreme sweating).

3. *Route of administration*: Insulin was usually administered by vein; occasionally it was given subcutaneously.

4. *The desired reaction*: At first, while the susceptibility and general reactivity of the patient were being observed, a brisk sweat was all that was sought. After 10 to 14 days, a state of drowsiness was produced. Occasionally, muscular twitchings were seen and rarely some convulsive movements. Tolerance seemed to be acquired quickly, so that a rising dosage scale was required when the intravenous route was used.

5. *Dosage*: The first dose was 10 units. This dose was increased by 3 to 10 units a day, depending upon the reaction obtained. Sometimes the same dose was re-employed for a few days, but soon the reaction failed to appear, and increases became necessary again. The dosage may rise to very high levels; in one case 180 and in another 190 units were used toward the end of the course. In those instances, reactions were difficult to obtain and, following a suggestion made by several authors, half the total dose was given at the beginning, followed by the other half in 30 minutes. This produced the desired reaction, although the total dose given at one time yielded only a feeble response.

When a second course was given, the dosage started again with 10 units, in the interests of caution.

A very important point concerning dosage is this: by the subcutaneous route, the dosage never greatly exceeds 40 units. Patients become sensitive to the insulin, and in later stages of treatment the dose level may be decreased. The intravenous route calls for much higher doses with slow, continual increases as treatment goes along. Doses as high as 190 units were reached in this series.

6. *Termination of individual treatments*: The patient was allowed to remain in the state of reaction for 30 to 40 minutes, after which the situation was terminated by the administration of orange juice. Glucose and a sterile 50 cc. syringe and needle were always kept at hand in case of emergency. In only one instance (Case 8) was the patient unable to take the orange juice. Glucose has been administered by vein 4 times nonetheless, in order to abort quickly what looked like too severe a reaction. The administration of sugar was followed by a short rest, after which the patient went out for breakfast.



TABLE I  
*Summary of treatment and results*

| CASE  | SEX | AGE            | PRES-<br>ENCE OF<br>ANX-<br>IETY OR<br>TENSION | DIAGNOSIS   | DURATION OF<br>TREATMENT              | DEGREE OF IMPROVEMENT |   |
|---|-----|----------------|--|---|---------------------------------------|-----------------------|---|
|   |     |                |  |   |                                       | Anxiety               | Total                                       |
| Systematic treatment  |     |                |  |   |                                       |                       |   |
| 1. W. B.  | M   | 41             | +  | Schizoid with delu-<br>sions                              | 1 series 5 wks.<br>1 series 8 wks.    | Marked<br>Marked      | Marked<br>Marked                            |
| 2. D. P.  | M   | 57             | +  | Anxiety, depression                                       | 10½ wks.                              | Marked                | Marked                                      |
| 3. L. D.  | M   | 70             | +  | Agitated depression,<br>moderate severity                 | 6 wks.                                | Moderate              | Moderate                                    |
| 4. A. H.  | M   | 69             | +  | Agitated depression,<br>moderate severity                 | 9 wks.                                | Marked                | Marked                                      |
| 5. L. S.  | F   | 52             | +  | Agitated depression                                       | 6 wks.                                | Marked                | None  |
| 6. L. A.  | M   | 58             | —  | Depression with de-<br>lusions (Also elec-<br>tric shock) | 7 wks.                                |                       | Moderate                                    |
| 7. A. R.  | M   | 21             | +  | Obsessional neurosis                                      | 13 wks.                               | Moderate              | Moderate                                    |
| 8. J. G.  | F   | 13             | —  | Hysteria  | 3½ wks.                               |                       | None  |
| 9. C. C.  | M   | 45             | +  | Anxiety state—real<br>basis                               | 3 wks.                                | None                  | None  |
| 10. B. S.   | F   | 23             | +  | Psychoneurosis, ano-<br>rexia nervosa type                | 8 wks.                                | Moderate              | None  |
| 11. L. K.   | M   | 19<br>to<br>23 | +  | Mixed schizoid with<br>obsessiveness                      | 11 wks.<br>3 wks.<br>4 wks.<br>6 wks. | Marked<br>?<br>?<br>? | Marked<br>None<br>Question-<br>able<br>None |
| Occasional, or a brief series (for the symptom of tension only) |     |                |  |   |                                       |                       |   |
| 12. M. A.   | F   | 44             | +  | Schizoid with delu-<br>sions                              | Intermittent                          | Marked                | None  |
| 13. M. P.   | F.  | 30             | +  | Schizoid paranoid   | 1 wk.                                 | Marked                |   |
| 14. G. S.   | F   | 35             | +  | Agitated depression                                       | Several                               | Marked;<br>None       |   |
| 15. L. S.   | F   | 32             | +  | Psychoneurosis  | 1 time                                | Marked                |   |
| 16. A. G.   | F   | 58             | +  | Psychoneurosis  | 4 times                               | Marked                |   |
| 17. M. K.   | M   | 49             | +  | Obsessional neurosis                                      | 3 wks.                                | Marked                |   |
| 18. E. M.   | F   | 52             | +  | Schizoid paranoid   | 3 wks.                                | Marked                |   |



7. *Untoward after effects:* (A) Delayed reaction, occurring later in the day. There have been none of these when the intravenous route was employed, except in one case (Case 8). When the technique was varied, and subcutaneous administration was employed, there was an occasional delayed reaction. Nonetheless, all patients were instructed to keep 3 lumps of sugar with them all day. (B) Fatigue and weakness for several hours. This was not uncommon following a brisk reaction.

8. *Length of course of treatment:* This varied considerably. The treatment may be used only occasionally, to relieve an acute access of anxiety. A consistent course of treatment lasts from 6 to 12 weeks, with an injection daily except Sunday.

As Table I shows, the cases treated were of various diagnostic categories. No schizophrenic or depressive patient was treated who was not considered safe as an ambulant patient, and all were able to continue working, although sometimes with difficulty. The intensity of tension was often great, in all types of patient.

As the table indicates, the majority of patients were improved by the treatment. Improvement occurred outstandingly in the symptom of tension. The decrease in tension was sometimes associated with improvement in the whole condition, but sometimes it was isolated, the rest of the symptoms remaining unchanged. The improvement in tension was frequently transitory; in cases with prolonged treatment, however, in which the basic illness was relieved, tension disappeared permanently.

#### ABSTRACTS OF CASES

*Case 1.* W. B., a man of 41, referred by Dr. Louis Soffer. Diagnosis: schizoid reaction. This patient suffered from a state of severe tension, accompanying a delusion that all four of his extremities were shrinking in size. The illness had followed a throat infection 5 months earlier. Of special interest was the fact that the right side had always been slightly but actually smaller than the left. The deep reflexes on the right were greater than those on the left at the time of examination. X-ray examination of the skull by the late Dr. C. C. Dyke, showed the left parietal bone to be thicker than the right, and the left supra-orbital ethmoid cell to be larger than the right; these findings were interpreted as suggestive of a mild left cerebral hypoplasia, dating from the patient's earliest years (Dyke-Davidoff-Masson syndrome). An electroencephalogram, made by Dr. Hans Strauss, was normal. The likelihood of finding anything except hypoplasia or a non-surgical cyst, was so remote that it appeared unnecessary to do a pneumoencephalogram, and this procedure was deferred in order to observe the effects of treatment. Insulin treatment was given daily over a period of 5 weeks, with marked improvement of the delusion and of the anxiety. Another course of treatment was commenced 2½ months later, this time for 8 weeks. The symptoms disappeared entirely and the patient remained well for a year, after which there was a mild recurrence. The largest dose of insulin was 140 units. The first dose in the second series was 10 units.

*Case 2.* D. P., a man of 57, was having what was considered his third moderately severe depression with anxiety in 3 years, with no clearcut symptom-free period between them. He had always been a seclusive, sober, hard-working man, devoid of gaiety and with no interests outside of his work. He was given a 10½ week course of insulin therapy, after which there was complete recovery from the depression, lasting 1½ years. Subsequently there was a mild recurrence. The largest dose of insulin employed was 40 units.

*Case 3.* L. D., a man aged 70 years, had been in his second agitated depression for about 10 months. Electric shock therapy had not yet come into generally accepted use for people

with arteriosclerosis as advanced as his. Improvement in both agitation and depression was moderate.

*Case 4.* A. H., a man of 69, referred by Dr. Eli Moschcowitz, had been in his second agitated depression for a month. The symptoms were moderately severe. Two electric shock treatments, given by Dr. Lothar Kalinowsky, resulted in prolonged apnea, and it was considered unsafe to continue with that type of therapy. The 2 treatments produced no relief. Insulin was given; no definite improvement occurred until about the 6th week. The treatment was continued for 9 weeks, the largest dose being 75 units. The patient made a complete recovery. There is some doubt in this instance that the insulin is to be credited with the recovery, which perhaps could have been a spontaneous one. Also notable is the fact that although the total and final result was excellent, each treatment produced an exacerbation, instead of a reduction in tension.

*Case 5.* L. S., a woman of 52, referred by Dr. Leonard G. Weber, had an agitated depression. Daily improvement of the agitation occurred in insulin treatment but the depression was unaffected. The agitation returned in full force when treatment was terminated.

*Case 6.* L. A., a man of 58, referred by Dr. Eli Moschcowitz, was in a depression with marked retardation and some dilapidation. Nine years previously he had been through a manic episode. Eleven electric shock treatments brought him out of the depression, but there was a complete relapse in a few weeks. It was decided to try the ambulatory insulin method as an alternative to resumption of electric shock. Treatment was given over a period of 7 weeks. This is one of the cases in which reactions were difficult to obtain and the divided dose had to be employed; toward the end, 95 units were given twice in an hour.

Recovery was satisfactory and the patient was able to return to his work as an engineer. The patient's condition was not as good, however, as it was in the brief period following electric shock.

*Case 7.* A. R., a man of 21, had a severe obsessional neurosis, with intense agitation and rather severe depression. The insulin was given over a period of 13 weeks. There was marked improvement in the affective symptoms, still maintained at the end of 2 years. The obsessive thinking was reduced somewhat, but not to a significant degree.

*Case 8.* J. G. was a girl of 13, a patient of Dr. Donald MacPherson. She presented a severe and complex hysterical reaction. There was no manifest anxiety. A major phenomenon was her refusal to eat, which had impaired her physical condition so greatly that hospitalization and artificial feeding were required. She improved while in the hospital but was still a seriously ill patient on discharge. Insulin treatment was begun in the hospital and continued after discharge. After a short series of injections, one day she failed to eat either breakfast or lunch after her treatment, as a dramatic gesture. Later in the afternoon she was found in stupor. She was revived and insulin treatment was terminated. There had been little or no improvement.

*Case 9.* C. C., referred by Dr. L. Jacobius, was a man of 45, with a longstanding history of fears, anxiety and hypochondriasis. A son had died of leukemia 3 years before. The patient himself now had leukemia. Efforts had been made to keep knowledge of the diagnosis from him but with questionable success. Many of his symptoms were similar to those of his son and he lived in terror of the truth. Insulin was given for 3 weeks, the largest dose being 80 units, but utterly without success in reducing the state of panic.

*Case 10.* B. S., a woman of 23, referred by Dr. David Hays. This patient had a psychoneurosis of many years standing. Her emotional life was almost limited to her relationship with her mother, and each attempt to expand her emotional interests led to symptom production. A series of phobias had also long marked the patient's emotional course. Insulin treatment had a pronounced and satisfactory effect upon the patient's tension state, but none upon the other symptoms.

*Case 11.* L. K. was a 19 year old boy with many schizoid manifestations, including the delusion that his hair was falling out, depression and states of panic. Insulin early in the illness was of profound help in reducing the panic. The illness had a long subsequent course and later insulin was without effect.

*Case 12.* M. A., a woman of 44, a patient of Dr. A. A. Epstein, had had a childhood psychosis, had never been free of depression since, and had now had isolated delusions of persecution for 7 years. She was seriously depressed and in an intense state of panic when first seen. She was sent to Blythewood Sanitarium for a course of insulin shock treatment, from which she returned greatly improved but not cured. Subsequently, 20 to 25 units of insulin were administered daily, by the subcutaneous route, for a period of a few weeks at a time. Invariably, the patient was markedly improved affectively, anxiety and feelings of panic being reduced. The insulin treatment was carried out by Dr. Epstein, who has kindly given me permission to include the case in this series.

Six other patients were also treated either briefly or occasionally, in some instances while psychotherapy was being conducted by someone else. Definite relief of tension was usually, but not invariably, obtained. In Case 14, treatment was sometimes markedly successful, and sometimes completely without effect.

*Comment.* The ambulant insulin technique has been employed in office practice in 18 cases of different varieties of emotional and mental disturbance.

In all cases, insulin treatment and psychotherapy were administered jointly. Many times the nature of the illness made intensive psychotherapy impossible to conduct and the psychological phase of the treatment was merely supportive.

The results are sufficiently regular and definite to warrant the conclusion that this mode of treatment is extremely useful in the treatment of severe states of tension. This finding coincides completely with those of other authors. In addition, there is no doubt, as others and Rennie in particular have pointed out, that as intense anxiety recedes, patients become more accessible and psychotherapy can be carried out more readily.

This series also adds to the evidence that the method may be used in the treatment of depression. It is much slower than electric shock. Possibly it is also less effective. Two cases (2 and 4) may be put down as cures, but in cases 3 and 6 the depression was merely improved, and in case 5, the depression was not improved at all. To be sure, Case 6 was a complicated one, but the improvement obtained from a single course of electric shock treatment was far more complete and striking while it lasted, than the help derived from insulin.

In Case 1, an isolated delusional system disappeared, probably as a result of treatment.

In none of the remaining cases was the basic illness affected. Conclusions cannot be drawn from this part of the result, however, because this series is obviously too small. The series gains its validity only from the almost regular relief of tension in varied kinds of cases.

Of special interest is Case 9. The state of panic had its foundation in reality; efforts to deny the patient knowledge of the diagnosis of leukemia were, at most, of questionable success. The patient had indeed been hypochondriacal and his ego interests had been over-centralized and neurotic. He must have incorporated his new, realistic terror into his well-formed personality structure, and combined it with his old hypochondriacal tendencies. But his panic state differs nonetheless from the others in the series in having at least a preponderantly conscious, real cause. It is therefore of interest to find this patient completely unaffected by insulin.

There appears to be no regularity in the speed with which the insulin begins to have a strikingly beneficial effect. It is true that most patients begin to feel

better as soon as the insulin dose is large enough to produce a reaction. Occasionally, a pronounced effect is obtained with the first dose. Some patients have to await very marked benefit until a fairly high dosage, with a brisk reaction, is attained. This coincides with the observations of Polatin and Spotnitz, who noted a cumulative effect in giving extended treatment for the treatment of hospitalized patients with psychoses (8).

In addition to a systematic course of ambulant insulin therapy, insulin may be administered occasionally either by vein or subcutaneously, to help patients over short periods of anxiety or panic.

#### SUMMARY

(1) The ambulant insulin treatment method of Polatin, Spotnitz and Wiesel has been employed in 18 cases of different types.

(2) The symptom of intense tension can usually be relieved, in whole or in part, by this treatment.

(3) This series adds a small amount of evidence to that more extensively accumulated by others, that the basic illness may be relieved by this method. This applies to schizophrenia and to depression.

(4) The treatment may be given either in occasional isolated doses or as a systematic procedure with increasing doses, extending over a period of weeks.

(5) The treatment is feasible for office use. After the injection has been given, no special set-up is required beyond the presence of a trained person to watch the patient and the presence of the doctor in the office.

(6) The dosage ranges are far lower with the subcutaneous than with the intravenous route of administration.

(7) The treatment cannot be used in the office with psychotic patients unless the manifestations are symptomatically mild. Patients should be hospitalized instead, if there is any question of risk in keeping them unhospitalized.

#### BIBLIOGRAPHY

1. POLATIN, PHILLIP, SPOTNITZ, HYMAN AND WIESEL, BENJAMIN: Effects of Intravenous Injection of Insulin in Treatment of Mental Disease. *Arch. Neurol. & Psychiat.*, 43: 925, 1940.
2. POLATIN, PHILLIP, SPOTNITZ, HYMAN AND WIESEL, BENJAMIN: Ambulatory Insulin Treatment of Mental Disorders. *New York State J. Med.*, 40: 843, 1940.
3. MACGREGOR, JAMES S. AND SANDISON, R. A.: Insulin Treatment of Schizophrenia in Wartime. *Brit. M. J.*, 2: 310, 1940.
4. TOMLINSON, PAUL J. AND OZARIN, LUCY D.: Ambulatory Insulin Therapy: A Report of Fifty-two Cases. *Psychiat. Quart.*, 16: 167, 1942.
5. COWIE, D. M., PARSONS, J. P. AND RAPHAEL, T.: Insulin and the Mental State of Depression. *J. Mich. State Med. Soc.*, 22: 383, 1923.
6. APPEL, KENNETH E., FARR, CLIFFORD B. AND MARSHALL, HAROLD K.: Insulin in Under-nutrition in the Psychoses. *Arch. Neurol. & Psychiat.*, 21: 149, 1929.
7. BENNETT, C. R. AND MILLER, T. K.: An Observation on the Treatment of Mental Cases with Sub-Shock Doses of Insulin. *Am. J. Psychiat.*, 96: 961, 1940.
8. POLATIN, PHILLIP AND SPOTNITZ, HYMAN: Continuous Ambulatory Insulin Shock Technique in Treatment of Schizophrenia. *Arch. Neurol. & Psychiat.*, 47: 53, 1942.
9. RENNIE, THOMAS A. C.: Use of Insulin As Sedation Therapy. *Arch. Neurol. & Psychiat.*, 50: 697, 1943.

# CHANGES IN THE PRECORDIAL ELECTROCARDIOGRAM DUE TO THE POSITION OF THE EXPLORING ELECTRODE

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In the course of the study of chest leads during the past years, certain inaccuracies in the technic of recording these leads have been suggested by variations in the chest lead pattern, not adequately explained by any change in the clinical condition of the patient. Since practically all chest lead procedures employ an apex position for at least one chest derivation, it seemed logical to direct an inquiry into the methods employed in determining the position of the apex. It was found in routine clinical examinations in the ward and in certain electrocardiographic investigations, that various individuals, including internes, residents and attending physicians had located and marked the apex, each according to the methods usually employed for this purpose by that individual. It was further early apparent that a rather wide range in the recorded apex position might be observed if skin marks of one observer were removed prior to the examination and subsequent apex localization of later examiners. Therefore, these patients were examined fluoroscopically with apex localization by the method usually employed in orthodiascopy, i.e. with a very small diaphragm aperture, in order to eliminate any distortion effect. Too often to be considered a mere coincidence, it was found that a considerable error occurred when an attempt was made to establish the apex position by any of the methods usually employed in physical examination for this purpose, namely by inspection, palpation of the apex impulse, or by percussion of the left cardiac border. It, therefore, appeared desirable to determine whether this apparent error might be the cause of a change in the chest lead pattern, and if so, how frequently and to what degree; and finally whether this factor might be of clinical importance. To this end a small series of observations on consecutive private patients will furnish the basis of this report. All of these patients were examined in the office by the author, all in the erect posture, in most instances standing.

Procedure: The apex impulse, if visible or palpable, was noted and marked with a skin pencil. The left cardiac border was then determined by percussion and marked with a different colored pencil. In order to eliminate error due to suggestion, this percussion and the marking of the skin was done with the eyes of the examiner closed. The patient was then examined fluoroscopically. With the small diaphragm aperture, the apex was located as exactly as possible. A metal instrument (uterine sound) was held on the skin at that point and an assistant marked the apex with a third colored pencil. During this entire fluoroscopic procedure, the examiner worked in the dark, or with eyes closed when the assistant required a light in order to mark the skin; thus the factor of suggestion due to preceeding marks was eliminated. Table 1 will show how great an error may occur with certain individuals, even when this examination is made by one of some considerable experience and competence in this field.



To the sceptic or that physician who is very certain as to his accuracy in this type of physical examination, the author suggests this method as an almost certain means of removing that diagnostic conceit which too often comes with professional maturity.

Electrocardiograms were then recorded, the patients sitting. The procedure advocated by Pardee (1) was employed for the chest leads, as it appears to have sufficient merit to justify its use clinically. Since Pardee's "position" 4 is at the cardiac apex, and "position" 3 lies midway between "position" 2 and 4, two sets of Pardee records were recorded, first with the apex as determined fluoroscopically, and then as determined by physical means.<sup>1</sup> It was found that usually the apex, if palpable, so nearly coincided with the left border as determined by percussion, that the small chest electrode (3 cm. diameter) covered both points on the skin, thus making duplication of records unnecessary. These curves, especially those from "position" 3 and 4 were then compared, and will be reported at a later point in this paper.

Since various factors may effect the form of the electrocardiogram, these factors will be discussed under the following headings, and pertinent literature quoted at this point.

1. Methods for the localization of the cardiac apex and possible errors in these methods.
2. The importance of the position of the patient during such cardiac examination, whether physical, x-ray, or electrocardiographic.
3. The effect of changes in the posture of the patient on any of these forms of examination.
4. The effect upon the electrocardiogram of change in the position of the chest electrode.

### 1. Cardiac apex localization

*By noting the apical impulse.* Opinion differs considerably regarding the advisability and value of this method. White (2) states, "To locate the position of the apex . . . is possible in the great majority of cases, failing only in a few obese or very sick patients" . . . "permits the identification of the maximum apex impulse as the site of the cardiac apex. This is usually in agreement within a few millimeters with the position of the apex as determined by orthodiagraphy." The mention of orthodiagraphy indicates that this author is considering the patient as in the erect posture, and it is in this position that the apical impulse is most frequently visible or palpable. Roesler (3) states, "The outermost limit of the *apical thrust* is the best clinical guide in evaluating the size of the left ventricle. In adults it is visible in not more than one-fifth of all cases, and it is rather uncommon to palpate it in the recumbent position." "It is neither seen nor felt in the obese and emphysematous" and "is feeble or not palpable in dilatation without hypertrophy." Practically the same view is expressed by

<sup>1</sup> In this paper no attempt is made to determine the relative merits of the various chest lead procedures which have been advocated. All are in some degree dependent upon the determination of the apex position.



Scherf and Boyd (4) who state, "The apical impulse is not palpable in the recumbent position in approximately four-fifths of adults" and "not much better in patients with hypertrophied left hearts." Luton (7) failed to locate the apex by either inspection or palpation in 5 of 19 elderly men. It is apparent from these references that there exists a wide divergence of opinion as to the value of this method of localization of the cardiac apex. The experience of most clinicians is that this is of limited value, especially in the type of individual who frequently presents himself for cardiac examination, v.s. the obese, emphysematous patient, oftentimes with a dilated feebly acting heart. In addition to these unfavorable factors must be added the effect of the well developed female breast, which in the majority of instances precludes satisfactory inspection or palpation of the apical impulse. All agree, however, that inspection and palpation of the cardiac impulse are of greatest value in the erect posture, and are of very limited value in the recumbent posture, a subject to be discussed in connection with a consideration of the position of the patient during the electrocardiographic examination.

*By determination of the left cardiac border by means of percussion.* This method as well as inspection and palpation of the apex impulse is found wanting by some, highly acceptable by others. Unfortunately the older concept of the two types of cardiac dullness, namely relative and absolute cardiac dullness, have only served to add to the confusion. Nearly twenty years ago, Pratt and Bushnell (5) wrote, "Even if the chest is normal, a strong percussion stroke will give a dull note far outside the vertical projection of the left border on the anterior surface." The results of varying degrees of percussion are shown in figure 25, page 288. They state, "It is evident that the percussion of relative dullness involves a *larger subjective element*." These authors also discuss the importance of fat and muscle layers and of the breasts in women, and state, "Serious errors in locating the heart borders are occasionally made by experienced physicians, the cause of which is unexplained." This statement regarding errors in percussion recalls the story told of the experience of Sir Thomas Lewis, who asked three well known clinicians to independently locate the heart borders on the same patient, following which these borders were marked with lead wires and then checked with the orthodiagram. None agreed although the differences were not great, perhaps due to the fact that the three competing physicians were three outstanding British clinicians of that day—Osler, MacKenzie and Allbutt. The "moderator" in this episode is unusually proficient in palpation of the cardiac apex. It is my impression both from personal observation of this clinician and from his writings that he places much greater reliance upon palpation than upon percussion in cardiac examination. Very recently White (2) in a discussion of the range of the normal heart has stressed the importance of body build and of extra-cardiac influences upon the results of percussion. It is probable that those physicians who place greatest reliance upon cardiac percussion are those who employ a uniform percussion stroke intermediate between that employed in light and heavy percussion. According to White (2) this "much neglected and often despised method" . . . "is of help in occasional cases when the apex impulse is felt with difficulty or not at all." King (6) finds a

very limited factor of error in percussion of the cardiac borders. He states, "Percussion may not be expected to permit determination of the heart with less than 0.5 to 1 cm. error on each border, left and right." This statement regarding the right border percussion is interesting in view of the recognized error in the right cardiac border percussion when checked by roentgenographic methods. Luton (7) found that percussion "yielded uniformly consistent figures—the left border being located at from 0.2–5 cm. (average 1.2 cm.) to the left of the apex beat", and reported a very limited difference between the results obtained by percussion and by the roentgenogram—an average difference of 1.5 cm. I checked this observation in a total of 58 individuals of various ages, body build and of both sexes. In 32 of these there was a difference between the palpable apex and/or the left border of the heart as determined by percussion, and the extreme tip of the apex by orthodiascopy, this difference ranging

TABLE I  
*Factors of Error in Apex Localization by Physical Examination*

|   |   |   |   |   |          |          |         |
|---|---|---|---|---|----------|----------|---------|
| Apex by physical examination and orthodiascopy identical in |   |   |   |   | 26 cases |          |         |
| "   | " | " | " | " | "        | 32 cases |         |
| Total.....  |   |   |   |   | 58 cases |          |         |
| Difference P. E. and Orthodiascopy.....                     |   |   |   |   | 1 cm.    | 11 cases | M 5 F 6 |
| "   | " | " | " | " | 2 cm.    | 6 "      | M 2 F 4 |
| "   | " | " | " | " | 3 cm.    | 7 "      | M 7     |
| "   | " | " | " | " | 4 cm.    | 6 "      | M 3 F 3 |
| "   | " | " | " | " | 6 cm.    | 2 "      | M 2     |
| Total.....  |   |   |   |   |          | 32 cases |         |

from 0.5 cm. to 6 cm. The average difference observed in this group of 32 was 2.54 cm. In 26 of the total of 58 persons examined by both the physical and orthodiascopic method there was no measurable difference. In only five of the total of 58 examined was a palpable apex encountered, although the patients were standing during the examination and an especial effort was made to find any point of localized apical pulsation on the chest which could be considered a point of maximum intensity of the apex beat. In several instances a diffuse pulsation was noted, but at no point sufficiently accentuated to represent the localized apex beat and hence the position of the apex. At least in my hands palpation for the localization of the cardiac apex appears of very limited value. On the other hand, when present there was reasonable agreement with the left border by percussion, in two cases absolute, in two a difference of only 0.5 cm., and in one 1 cm. difference. This agreement in this small group of 5 cases was no guarantee that the apex would be found at the same point by the orthodiascope, for none entirely agreed; three varied 1 to 2 cm., and in one in which the palpation and percussion points were identical the apex was found 3 cm. to the right of these points. In this series the female breast appeared not to be an important cause of error, for, as will be seen in Table 1, where a difference of 3 cm. or greater occurred, the ratio of males to females was 4:1. Difficulty

in location of the apex is recognized by the Committee for Standardization (20) which states in its last report, "When the apex beat cannot be satisfactorily located. . . ."

It appears that inspection, palpation and percussion as employed by certain highly trained and proficient physicians are of value in locating the cardiac apex, but that the factor of error may be considerable and of clinical significance. In certain instances one or even all of these procedures may fail to locate the apex with accuracy sufficient for clinical purposes (see White (2) page 183). Under the best examining conditions these physical methods are very unsatisfactory in the fat individual. The accuracy of any of these methods in the individual patient is readily determined by the use of lead wire carefully applied with an adhesive over points marked on the skin and in conjunction with the orthodiascope. This x-ray method is more accurate than the teleroentgenogram due to the slight distortion in the latter, this factor of error not existing in the orthodiagram. Moreover, the teleroentgenogram often fails to clearly outline the apex due to an existing fat-pad, high diaphragm or slight rotation, while the orthodiascope permits accurate location.

## *2. Importance of position of patient during the physical, roentgen or electrocardiographic examination of the heart*

All available evidence indicates that both palpation of the apical impulse and percussion of the left border are most successfully carried out with the patient standing or sitting (preferably the former), due to the shift which occurs with recumbency when the heart is not anchored by adhesions, or held in place by surrounding masses or fluid. Since these same factors are of equal importance, and in like manner during roentgenographic examination of the heart, it follows that such examination will be most satisfactory when made in the erect posture. Certainly the practice of apex impulse and/or heart border delineation with the patient in the recumbent posture followed by roentgenographic or fluoroscopic control with the patient in the erect posture is to be condemned, although exactly this procedure is frequently employed in hospital practice.

Regarding the *position of the patient* (sitting or recumbent) *during the recording of the electrocardiogram*, there is no uniformity of practice. In the majority of the reports studied no mention is made of the position of the patient during the recording of the curve—excepting in those papers dealing specifically with alterations in the curve associated with changes in posture. To date there appears to be no position adopted on the subject as standard, although a change in the form of the curve with change in posture is recognized. In the fourth edition of "Nomenclature and Criteria for Diagnosis of Diseases of the Heart," the suggestion is made that the posture employed be recorded, but there is no recommendation as to which posture is preferable even in the case of the office ambulant patient. In its last report (20) released in April, 1943, The American Committee for Standardization discusses "dissatisfaction with routine apical leads" yet there is no statement as to how the apex is to be located nor the

position of the patient during the recording of the electrocardiogram. Since the cardiac apex serves as a focal point in either the single or multiple precordial lead procedure, and since this has been shown to shift with the adoption of the recumbent posture, unless this shift is prevented by associated pathology, it appears logical that the same erect patient position should be routinely employed in the ambulant patient during the recording of the electrocardiogram, as during physical and x-ray examination. It is recognized that occasionally in the asthenic individual, and especially one with a long thorax, the recumbent posture may be required in order to evaluate the importance of an inverted  $T_2$ . It is likewise true that certain seriously ill patients cannot be examined in other than the recumbent posture, but since the vast majority of records are made on patients who can at least sit in bed, it would seem that the most favorable posture should be employed where possible. In addition to this difficulty in the placing of the electrode at or in relation to the apex and some other point on the chest when the patient is in the recumbent posture, there is an added reason for the abandonment of the recumbent posture during the electrocardiogram registration.

### 3. *The effect of change in posture*

Numerous observers have reported *Changes in the form of the Electrocardiogram with a change or changes in posture*. Not all of these are in agreement, but the fact appears to be established that *significant changes of possible diagnostic importance* may occur with no greater change in conditions than the position of the patient during the recording of the curve. Mayerson and Davis (8) studied the effect of a passive change from the recumbent to the upright ( $75^\circ$ ) position in 10 normal subjects. They attributed changes in the curve to a "shift in the position of the heart and an alteration of its contacts with neighboring tissues." Schloma and Reindell (9) found that on having the patient stand the QRS becomes smaller and the T wave becomes notched and diphasic, and suggested that the degree of this change might be used as a functional test of the heart. Scherf and Weissberg (10) considered the importance of T wave inversion and S-T depression on changes in posture and the possible significance of these changes and their value as evidence of a myocardial lesion. They attributed these changes as solely dependent "on posture and the position of the heart in the thoracic cage" and therefore of no value as signs of functional deficiency. According to White (2) "Certain changes of body position and of height of the diaphragm cause considerable shifting of the position of the apex impulse—the result is somewhat like that caused by *deep inspiration*. The effect on the electrocardiogram is very variable but usually not marked." In another article this author (11) states that " $T_2$  inversion occurs with change from *supine* to *standing*, and that it may be abolished by deep expiration." He believes that "the *height of the diaphragm* is almost, if not quite as important a factor as is body position." Stewart and Bailey (12) studied 16 patients employing, in addition to the three standard leads, three precordial derivations, v.s. mid-sternal at the fourth intercostal space, at the apex, and at a point halfway

between these two. It appears that the apex was located by palpation or percussion since no mention is made of x-ray control. Each of these was taken in three positions v.s. supine, sitting in bed (angle 90°), and lying on the left side. These investigators found that "the form of the chest lead varies with change in posture—regardless of the size of the heart or the deviation of the electrical axis. The changes were less marked in cases of chronic constrictive pericarditis—the general trend was toward progressive decrease in the amplitude of the R and T waves, as the subject's position was changed from supine to sitting, to lying on the left side." The T waves in some cases became diphasic instead of positive, and negative instead of diphasic. On change in posture from recumbency to standing, according to Sigler (13) the changes in some cases were "so marked as to make the electrocardiogram appear abnormal, and to lose its identity with those taken in other postures" in the same case. Individuals with abnormal hearts showed no greater changes than those with normal hearts. Sigler rejected the explanation of such changes in the electrocardiogram as on the basis of change of the position of the heart, but suggests that the variations in the curve are due to "changes in the conducting media surrounding the heart", or "due to differences in the mode of spread and retreat of the current." He especially stresses "*the importance of knowing the posture in which a tracing was taken before any pathological significance is applied to it.*" Leach, Reed and White (14) analysed 300 cases showing low voltage of the QRS complex in the conventional leads, the fourth lead alone, and in all four leads. In addition to "generalized debilitating diseases" they found "*changes in the position of the heart*" to be a factor in the production of low voltage of the QRS complexes and that "the thickness of the chest wall and the *position of the precordial electrode* influenced the voltage of the QRS in Lead IV." They concluded that this finding alone has little or no diagnostic value. In a report which appeared shortly after this, Bellet and Kershbaum (15) came to an opposite conclusion. They considered that "low voltage in the precordial leads is almost always associated with a severe grade of myocardial damage", but that "we should not rely upon a single precordial lead for a diagnosis of low voltage, and that this may only be considered acceptable when present in several chest leads."

#### 4. *The effect of change in the position of the precordial electrode*

In a study of sixty-seven patients Edwards and Vander Veer (16) showed that wide variations in the amplitude of R and S occur *as the exploring electrode is moved laterally*, the R wave increasing, the S wave decreasing. In normal hearts this *change is slight*, in enlarged hearts *often striking* and may be quite sudden and marked with *only a slight change in the position of the precordial electrode*. A complete change from abnormal in the medial positions to normal in the axillary positions was seen in several of the patients with diseased, enlarged hearts.

In this series the *effect of change in the position of the exploring electrode* was as follows: Of 30 cases (18 males—12 females) in which there existed a



difference between the apex position as determined by palpation and/or percussion and the apex as located with the orthodiascope, there were 7 in which there were wide or clinically significant differences in the electrocardiograms taken at these varying points; of these seven, 5 were females, 2 males. In 7 cases, of which 5 were males, electrocardiograms taken at the varying points were identical. In 16 cases (10 males—6 females) there were slight differences, mainly in the amplitude of the T waves (figs. 4 and 5). In some instances this was considerable but in none of these was there any deviation in the S-T segment or a change in the direction of the T waves. Differences of this degree would not appear to be of much clinical significance. It should be pointed out,

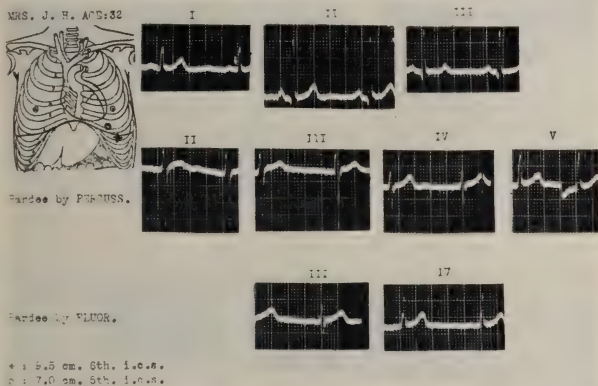


FIG. 1

however, that no greater changes than those occurring in these 16 patients have furnished the basis of clinical conclusions in certain published articles in the past, and from this standpoint are of importance. Of the 7 cases which showed changes which were considered as clinically significant, and therefore a source of serious error, analysis showed S-T deviations in 2 (figs. 1 and 2), marked differences in the T wave voltage in 3, and T wave inversion in 2 (fig. 3). In this group the difference between the apex positions varied from 1 to 6 cm. The extent of the variation appears not to be important, since the most marked changes were noted in 2 women and 1 man with variation in apex positions of 1 and 2 cm. only. In 7 instances the curves taken from differing positions on the precordium were identical, although in this group were differences in positions as great as 4 cm. in the case of a man aged 75; in one a difference of 3 cm; two of 2 cm., and three of 1 cm. It appears that chest contour and certain other extracardiac factors may be of as great importance as the actual heart size in determining the form of the precordial electrocardiogram.



There appears to be no acceptable evidence as to the permissible range of variation in the position of the precordial electrode and the *effect of such variation upon the curve*. The multiplicity of techniques offered for the recording of chest leads is indicative of the confusion which exists in this field. White (2)

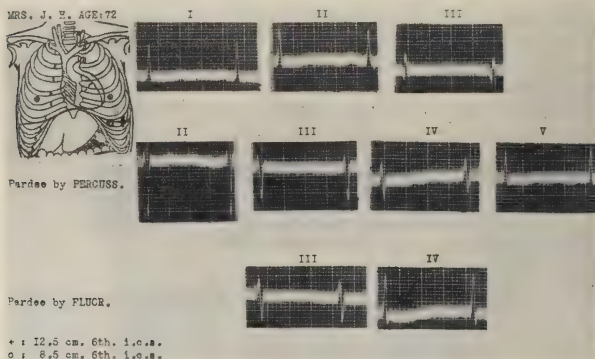


FIG. 2

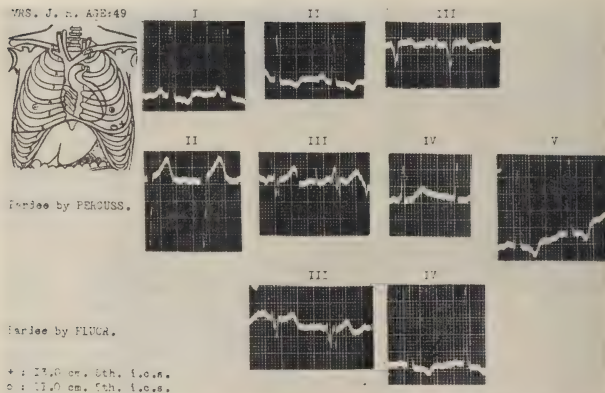


FIG. 3

appears to have had this in mind when, in a discussion of the fourth lead, he wrote, "It is essential for accuracy that the electrode be placed *directly* at the cardiac apex, both on the first occasion and at later examinations when the records will be compared, a requirement often neglected." He has recently written, "A study—of a change in the chest lead patterns with change in position

f the heart along with possible errors in location of the apex—is long overdue.” Personal communication July 27, 1944)<sup>2</sup>. Numerous authors have and still do

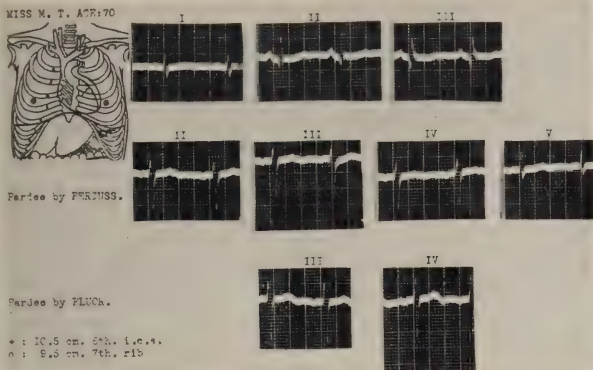


FIG. 4

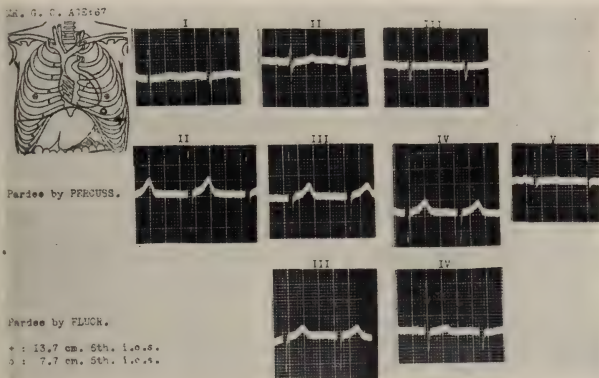


FIG. 5

employ the apex position for at least one precordial lead and attach considerable significance to the form of the resulting curve. In 1940 Wolferth and Wood

<sup>2</sup> Since this paper was submitted, Dr. Paul White writes, "Here at the Massachusetts General Hospital we have become so convinced of the importance of the localization of the electrodes that we have largely given up Lead 4 and take, whenever we need precordial leads, the following three— $CF_2$ ,  $CF_4$ , and  $CF_6$ ."

(17) stated, "Our studies of control groups suggest that when the precordial electrode is placed over the apex, an inverted T wave in the C F lead rarely occurs when the heart is normal." Yet exactly this was encountered in 2 instances in the present investigation. In the case of Mrs. J. H. age 49, this occurred when the electrode was directly over the heart apex as determined by fluoroscopy, not in the position as determined by percussion. The difference between the two points of electrode application was 2 cm. in the same intercostal space. In a second case T wave inversion occurred in the position determined by percussion, while at the fluoroscopic apex but 1.5 cm. away in the same space, this wave was upright. In its first report (18) in 1938 the Joint Committee of the American Heart Association and the Cardiac Society of Great Britain and Ireland stated, "It is recommended that those who employ a single precordial lead place the electrode upon the extreme outer border of the apex beat, as determined by palpation. If the apex beat cannot be located satisfactorily by palpation, it may be placed in the fifth intercostal space just outside the left border of cardiac dullness, or just outside the left mid-clavicular line, if percussion of the heart is unsatisfactory." In a Supplementary Report (19) which was released shortly thereafter by the American Committee, the apex position is again employed, for the following statement appears: "It shall be understood that . . . the precordial electrode has been placed upon a line drawn from the left sternal margin in the fourth intercostal space to the outer border of the apex beat (or to a point at the junction of the mid-clavicular line and the fifth intercostal space)." Five years later the same Committee (20) in an attempt to eliminate some of the existing confusion wrote, "When single precordial leads are taken from the outer border of the apex beat, the exploring electrode is, in actual practice, sometimes placed to the right of the region of transition mentioned, and sometimes to the left of or within it." "In serial observations on the same subject *inaccuracy in placing this electrode* or an alteration in the size or location of the region in question *may be responsible for striking changes in the form of the curve* obtained by what is technically the same lead." White (2) offers an explanation for these apparent discrepancies when he writes, "The fourth and fifth special precordial leads, although relatively close together, are often very different since they may overlie different ventricles or at least myocardial areas in very different states of health and disease." Whatever the explanation, it is clear that the most accurate localization of the apex (or any other cardiac focal point) possible, will be conducive to clinical accuracy. If this statement is incorrect it would seem that any precordial lead procedure which depends upon cardiac apex localization should be abandoned, and precordial leads should be limited to a right and/or left sternal border position and one near the apex—no attempt being made to place the electrode both over and at a point in relation to the apex and some other point. No claim is made in this paper that any specific or all chest lead procedures are in error, nor can the frequency of such error be stated from the limited number of cases studied. It does appear significant, however, that slight differences in the position of the precordial electrode may give such variations in the curve as

found in the seven cases mentioned above, which showed variations which would ordinarily be considered of clinical significance.

#### SUMMARY

Accurate location of the cardiac apex is difficult or impossible by any method save by the roentgen examination. Of roentgen procedures the orthodiascopic appears most reliable for this purpose. When, in recording precordial leads, the cardiac apex is used as a position for the application of the exploring electrode or as a point in relation to which other lead positions are established, the position of the apex should be determined by the orthodiascopic method. If this is not done, frequent and at times significant changes in the electrocardiographic curve may result. There are undoubtedly other causes for errors encountered in the recording of apical leads but this inaccuracy in location of the apex appears to be of considerable importance. This limited study appears to justify further inquiry as to the frequency and extent of variations which may occur in the precordial electrocardiogram with slight changes in the position of the exploring electrode. For the present, conservatism in the interpretation of the precordial lead curve appears desirable whenever any doubt exists as to the apex position.

#### BIBLIOGRAPHY

1. PARDEE, HAROLD E. B.: *Clinical Aspects of the Electrocardiogram*. ed. 4, New York, Paul B. Hoeber, Inc., 1941.
2. WHITE, PAUL D.: *Heart Disease*, ed. 3, New York, The Macmillan Company, 1944.
3. ROESLER, HUGO: *Diagnosis and Treatment of Cardiovascular Diseases*, Stroud, Philadelphia, F. A. Davis & Co., 1940, vol. 1.
4. SCHERF, DAVID AND BOYD, LINN J.: *Cardiovascular Diseases*, London, W. Heinemann, 1939.
5. PRATT, JOSEPH H. AND BUSHNELL, GEORGE E.: *Physical Diagnosis of Diseases of the Chest*, Philadelphia, W. B. Saunders Co., 1925.
6. KING, JOHN T., JR.: *Diagnosis and Treatment of Cardiovascular Disease*, Stroud, Philadelphia, F. A. Davis & Co., vol. 1.
7. LUTON, S.: Comparison of methods used for estimating the size of the heart. *South. M. J.*, 23: 681, 1930.
8. MAYERSON, H. S. AND DAVIS, W. D.: The influence of posture on the electrocardiogram. *Am. Heart J.* 24: 593, 1942.
9. SCHLOMKA, G., AND REINDELL, H.: Concerning the clinical electrocardiography. V. The changes in the curve with shift from the reclining position to standing. *Ztschr. f. klin. Med.* 130: 313, 1936. Abs. *Am. Heart J.* 14: 626, 1937.
10. SCHERF, DAVID AND WEISSBERG, JONAS: The alterations of the T-waves caused by a change of posture. *Am. J. M. Sc.* 201: 693, 1941.
11. WHITE, PAUL D., CHAMBERLAIN, FRANCIS L., AND GRAYBIEL, ASHTON: Inversion of the T-waves in lead II caused by a variation in position of the heart. *Brit. Heart J.* 3: 233, 1941.
12. STEWART, HAROLD J. AND BAILEY, ROBERT L.: The effect of posture on the form of precordial leads of the electrocardiogram. *Am. Heart J.* 18: 271, 1939.
13. SIGLER, LOUIS H.: Electrocardiographic changes occurring with alterations of posture from recumbent to standing positions. *Am. Heart J.* 15: 146, 1938.
14. LEACH, C. EDWARD, REED, WELFORD C. AND WHITE, PAUL D.: Low voltage of the QRS waves in the electrocardiogram, with special reference to lead IV. *Am. Heart J.* 21: 551, 1941.

15. BELLET, SAMUEL AND KERSHBAUM, ALFRED: The significance of low voltage of the QRS complex in precordial leads. *Am. Heart J.* 22: 195, 1941.
16. EDWARDS, JOSEPH C., AND VANDER VEER, JOSEPH B.: A study of the chest leads of the electrocardiogram with an evaluation of the positions of the precordial electrode. *Am. Heart J.* 16: 431, 1938.
17. WOLFERTH, C. C., AND WOOD, F. C.: The prediction of differences between precordial leads, CR, CL, and CF, based on limb lead findings. *Am. Heart J.* 20: 12, 1940.
18. Standardization of Precordial Leads: Joint recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland. *Am. Heart J.* 15: 1, 107, 1938.
19. Standardization of Precordial Leads. Supplementary report. *Am. Heart J.* 15: 2, 235, 1938.
20. Second Supplementary Report by the Committee of the American Heart Association for the Standardization of Precordial Leads. *Am. Heart J.* 25: 4, 535, 1943.



## THE RELIABILITY OF SEROLOGIC TESTS FOR SYPHILIS<sup>1</sup>

LOUIS CHARGIN, M.D., AND CHARLES R. REIN, MAJOR, M.C., A.U.S.

Every practicing physician has probably encountered instances of syphilitic patients who quite unaccountably gave a negative reaction where a positive one was to be expected and other instances of nonsyphilitic patients whose blood unexpectedly gave a positive reaction. Since the diagnosis and treatment in many cases hinges solely upon the serologic results such discrepancies are not only disconcerting but now and then may prove serious. When Wassermann (1) originally described the complement fixation test for syphilis it was thought to be based upon a true antigen-antibody reaction. It was considered specific for syphilis and regarded as due to the presence of spirochetes contained in the extracts of tissues (syphilitic liver) then employed as antigens. It was, however, soon discovered that not only were these antigens nonspecific, but that lipoid material prepared from normal, nonsyphilitic tissue (thus free from spirochetes) were even better antigens than those obtained from syphilitic material. The same situation with respect to antigens later proved to be true for the various precipitation (flocculation) tests subsequently developed (Kahn, Kline, Mazzini and others).

In view of this antigen nonspecificity, the serologic tests can hardly be looked upon as true antigen-antibody reactions and, therefore, as not truly specific for syphilis. The most that can be claimed for any of the serologic tests (whether it be a complement fixation or a precipitation test) is that nearly every syphilitic patient shows a positive result in varying degree (high or low titre) at one time or another in the course of their disease and they are, therefore, highly diagnostic for syphilis. But in the course of time it has been discovered that a number of diseases and pathologic states (other than syphilis) may occasionally or frequently and at times persistently give positive serologic reactions just as in syphilis. Yet the most painstaking examination fails, in these cases, to detect the slightest evidence of syphilis. These instances are the so-called biologic false positive serologic reactions. If one takes into consideration the great number of individuals now being subjected to routine serologic examinations it is no great rarity for false positive reactions to be observed. The finding of such false positive tests often complicates the diagnostic problem, and just as often poses the question whether or not the patient has in fact syphilis. Moreover, on the basis of such false positive serologic reactions alone many persons have been stigmatized as syphilitic, and what is infinitely worse many have been and are being subjected needlessly to antisyphilitic therapy.

While technical errors may account for some false positive reactions it has now been determined that this does not hold true for the majority of cases. It is now well recognized that something in the blood of some individuals and in cer-

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tain normal animals is the cause of such false positive reactions. This seems to be due to the existence of reagin or some antibody-like substance in the serum as a result of certain diseases and pathologic states, which gives positive reactions with the serologic tests for syphilis.

Various attempts to render the tests more specific for syphilis by variation of the antigens have thus far resulted in failure. It was thought that the introduction of an antigen from cultures spirochetes, that is, "specific" antigen in the true sense, would solve the specificity problems. Unfortunately this too has been unsuccessful since false positive reactions have also been obtained with such antigens.

A number of procedures, other than refinements in the antigens, have been introduced in an attempt to overcome this difficulty, that is to differentiate between the true and false positive reactions. Among the earliest of these are those of Hecht (2), Wassermann (3) and Witebsky (4). These earlier "confirmation" tests as they have been named have been subjected to more or less extensive trials and also found wanting. More recently Kahn (5) has introduced several procedures to differentiate true from false positive reactions, so called Kahn verification tests. Kahn classified the types of reactions obtained with his various verifications tests as:

a. "*Syphilitic Type*"—a pattern observed by Kahn in known syphilitic individuals.

b. "*Biologic False Positive (Nonsyphilitic) Type*"—a pattern observed by Kahn in nonsyphilitic individuals and in certain animals.

c. "*Inconclusive Type*"—Those patterns which do not conform to either of the above.

If we are to evaluate serologic reactions on the basis of Kahn's classification then we must require that syphilitic serums invariably give the syphilitic type of reaction and the nonsyphilitic serums give the false positive type of reaction. However, what has experience shown? It has been demonstrated that early and treated *syphilis* subjected to the verification test usually give the false positive type of reaction. On the other hand, blood from individuals in whom there is not the slightest reason for assuming syphilis has given syphilitic types of reaction. Furthermore, in some of the latter group the blood became persistently negative in a relatively short period of time without any antisymphilitic treatment, indicating that they were not the subjects of syphilis.

An extensive study of Kahn's first verification test (heat differential technique) (6) has shown that it too had the limitations of the earlier test (2, 3, 4) mentioned above. It too fails always to differentiate the true from the false positive reactions, especially in those instances where dependence for diagnosis necessarily rests on the serologic reaction. The same remarks also hold true for his more recent "triple-quantitative" and "salt dispersibility" techniques.

It may, therefore, be stated that at the present time there is no laboratory procedure which can be depended upon to differentiate the true from the false positive reactions. This being so, it is necessary to become aware of diseases

which may give a false positive reaction. This will serve at least to aid us in making a more correct diagnosis in evaluating an unexpected routine serologic reaction.

As stated at the outset, it has been known for a long time that certain diseases are capable of producing false positive reactions. With increasing experience, the number of such diseases is being added to and it is of paramount importance that the diseases in question become known to the practicing physician. This knowledge will lead to greater caution on the part of the practitioner in evaluating serologic reactions.

Perhaps the most frequent occurrence of such false positive reactions is in the upper respiratory diseases and in pneumonia. It has been found that as high as 20 per cent give false positive reactions in varying degree. These reactions are first detected 7 to 14 days after the clinical onset and may persist for many months. It is known that the severity of the disease bears no relationship to the occurrence or degree of positivity.

Immunization of various types, particularly cowpox vaccination, is a frequent source of false positive reactions. Five to 35 per cent of individuals who develop a "take" following the vaccination will develop false positive reactions. This usually appears 7 to 14 days after the "take", may be of high titre and may persist as long as four months. Tetanus, typhoid and other forms of immunizations may also be sources of false positive reactions but to a lesser degree than cowpox vaccinations.

Infectious mononucleosis and obscure fevers may also be associated with false positive reactions, although there is considerable difference of opinion as to the incidence. It is variously given as from 5 to 20 per cent differing with the type of serologic test performed. It should be pointed out that there is no relationship between the titre of heterophile reaction and the titre of false positive reaction.

Among the exanthems, measles and scarlet fever may give false positive reactions. Virus diseases, particularly virus pneumonia, and lymphopathia venereum may show false positive reactions. The incidence of false positive reactions associated with virus pneumonia has been stated to be as high as 25 per cent. Although tuberculosis has been mentioned as frequently associated with a false positive reaction, recent investigations disprove this.

In acute lupus erythematosus occasionally a false positive serologic reaction is observed.

Various serologic surveys have shown that as high as 50 per cent of patients affected with malaria will give false positive reactions. Members of the Armed Forces returned from highly endemic areas will have some relapses and may be the source of additional cases. Therefore, malaria may, in the future, more frequently be the cause of false positive reactions in this country. Among the diseases not common in our climate, that are usually associated with false positive reactions are leprosy, rat-bite fever, leishmaniasis, Weil's disease, recurrent fever and spotted fever.

The diseases just discussed by no means include all in which a false positive biologic reaction may be observed. On rare occasions, other diseases may show such a reaction.

There are a number of factors which are associated with the occurrence of false positive reactions, that should be borne in mind in considering unexpected reactions. They are, briefly:

1. *Serologic Reactors*: Certain individuals are more likely to develop false positive reactions than others under identical circumstances. This is probably due to some alteration or lability of their sero-globulins.

2. *Type of Serologic Test Employed*: This undoubtedly plays a role in the incidence of false positive reactions. In malaria, for example, the Hinton test shows a lower incidence than the Kahn, Kline or Kolmer tests. On the other hand, upper respiratory infections and immunizations produce fewer false positive reactions with the Kolmer complement fixation test than with the flocculation tests.

3. *Type of Disease*: The disease also plays a role, since it has been shown that leprosy and malaria may give 50 to 80 per cent false positive reactions whereas tuberculosis by comparison gives only 1 to 3 per cent such reactions.

4. *Frequency of Performing Tests*: It has been found that the incidence of false positive reactions is directly proportional to the frequency of performing the tests. The more often the tests are performed, the higher will be the incidence of detected false positive reactions.

In general it can be stated that in the vast majority of cases false reactions are of low titre and usually disappear in a relatively short period of time. Thus repeated serologic examinations will show a gradual decrease in the titre. They often show varying degrees of unaccountable fluctuation on repeated examinations. On the other hand high titre false reactions persisting over a long period may occur and it is particularly these instances that constitute the difficult cases in diagnosis. It is in such cases that it is often impossible to answer the question "Syphilis or not?"

The occurrence of an unexpected positive reaction should, of course, prompt a full investigation of the case. Among the procedures that should be followed in the investigation are a careful *detailed history* including questions as to prior genital or persistent genital lesions, non-pruritic persistent eruption, characteristic alopecia, dates and results of previous serologic examinations, prior anti-syphilitic treatment; also whether the patient ever had any of those diseases or conditions enumerated above which may cause false positive reactions. The individual should be subjected to a *complete physical examination* special attention being given to tell-tale scars, pigmentation, atrophic areas, Hutchinsonian teeth, healed interstitial keratitis, aortic disease and hemiplegias particularly in young individuals; *x-ray studies* of the cardiovascular and osseous systems for evidence of past or present syphilitic involvement; *serologic examinations* of parental bloods, particularly the mother's, of contacts, of their siblings and the patient's children; *spinal fluid examination* for evidence of asymptomatic neurosyphilis;

*repeated laboratory examinations* to rule out those affections which may cause false positive reactions. This list is by no means complete but will serve as a guide for the necessary approach.

#### CONCLUSIONS

1. The serologic tests for syphilis in use today are not truly specific.
2. False positive reactions are observed in a variety of nonsyphilitic diseases and conditions. The physician should be constantly aware of this fact in evaluating positive tests. He should make himself aware of the diseases that are likely to give false positive reactions.
3. There is no laboratory procedure at this time which will invariably differentiate between the true and the false positive serologic reactions for syphilis.
4. The need for a specific test for syphilis or for a dependable "verification" test is urgent.
5. The diagnosis of syphilis should not be made solely on unconfirmed positive serologic reactions and treatment should be withheld until such a diagnosis is definitely established.
6. Individuals with unconfirmed positive serologic reactions should be subjected to a careful history, a thorough physical examination, and to various other laboratory procedures to establish or rule out the existence of syphilis.
7. All findings, clinical and laboratory, should be evaluated in an effort to establish a diagnosis of syphilis.
8. It is factual to state that in a small percentage of cases it is impossible to decide whether or not syphilis exists in spite of the most careful and detailed study of the history and the clinical and laboratory data.

#### REFERENCES

- (1) WASSERMANN, A., NEISSNER, A., AND BRUCK, C.: Eine Serodiagnostische Reaktionen bei Syphilis. *Deutsche med. Wehnschr.*, 32: 745, 1906.
- (2) HECHT, H.: *Prag. Med. Wehnschr.*, 39: 316, 1914; *Deutsche. med. Wehnschr.*, 47: 1487, 1921.
- (3) WASSERMANN, A. V.: *Berl. Klin. Wehnschr.*, 58: 9 and 193, 1921; *Klin. Wehnschr.*, 1: 1101, 1922.
- (4) WITEBSKY, E.: *Ztschr. f. Immunitätsforsch. w. Exper. Therap.*, 80: 323, 1933.  
 ———; A confirmation test for the serodiagnosis of syphilis. *Arch. Path.*, 26: 1083, 1938.
- (5) KAHN, R. L.: A serologic verification test in the diagnosis of latent syphilis. *Arch. Arch. Dermat. & Syph.*, 41: 817, 1940; *Am. J. Syph., Gonorr. & Ven. Dis.*, 25: 151, 1941.  
 ———: A new verification method in serology of syphilis. *Univ. Hosp. Bull., Ann Arbor*, 8: 45, 1942.  
 ———: The verification test in the serology of syphilis. *Hour. Lab. & Clin. Med.*, 28: 1175, 1943.
- (6) CHARGIN, L., AND REIN, C. R.: The Kahn verification test. An appraisal of the test based on clinical and serologic evidence. *Arch. Dermat. & Syph.*, 44: 1031, 1941.

## SPINAL EXTRADURAL ARACHNOID CYST ASSOCIATED WITH EXTRADURAL MALIGNANCY

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Aside from the multiple lesions in von Recklinghausen's disease, multiple tumors of the central nervous system are of infrequent occurrence. Comparatively speaking multiple growths are more often encountered within the cranial cavity than within the spinal canal. Multiple meningiomas both over the convexity and within the ventricles have been reported, as have bilateral acoustic tumors and even multiple gliomas. Simultaneous growths involving the brain and the spinal cord have also been recorded. The association of intraspinal tumors and protruded intervertebral disks has recently been reported from the Mayo Clinic (2). In over 150 operations for spinal cord tumors I have encountered multiple tumors but twice. One instance was that of two meningiomas arising from the inner surface of the dura in the mid thoracic region. They were on opposite sides of the cord and separated by about one and a half cord segments. The other case to be here reported had at the 8th thoracic vertebra an extradural arachnoid cyst and at the level of the 10th thoracic vertebra an extradural neuro-(sympatico) blastoma.

### CASE REPORT

*History:* M. R. (Adm. #524096), a 48 year old housewife was admitted to The Mount Sinai Hospital on August 22, 1944. For three months prior to admission she had complained of pains in the left lower thorax and in the left upper quadrant of the abdomen. For five weeks she had been obstinately constipated. The first of several gastro-intestinal x-ray examinations had suggested an obstructing lesion which was not confirmed on the subsequent studies. An abdominal exploration was carried out without disclosing any lesion. When the patient was allowed out of bed it was noted that she could not stand because of weakness of the legs. Over the ensuing couple of days a complete paraplegia developed.

*Examination:* On September 19 examination showed a small gibbus at the tenth thoracic vertebra. There was a complete flaccid paraplegia. The deep reflexes in the lower extremities were just obtainable. The abdominal reflexes were all absent; there was absence of plantar flexion bilaterally. Position sense was absent in the toes, vibration was absent to the free border of the ribs. There was a rather indefinite level to pain at the tenth thoracic dermatome, with a small belt of hyperaesthesia above this. Spine tenderness was present over the ninth and tenth thoracic spines. A lumbar puncture yielded xanthochromic fluid with a complete manometric block. The fluid contained 284 mg. per cent total protein. Roentgen examination of the spine showed partial destruction of the pedicle of the tenth thoracic vertebra with a soft tissue mass lying along side of it. After the operation a second small area of bone absorption was noted on the right side of the eighth thoracic pedicle (fig. 1).

*Course:* On September 21 a laminectomy was carried out. Opposite the eighth thoracic vertebra was a thin walled cyst containing clear fluid. It measured about an inch and a half in length by about three quarters of an inch in the other two diameters. It lay on the dura a bit more to the right than the left. It was readily picked up from the dura and a very small neck led inside the dura just to the right of the mid line. To the left of the exposed dura, opposite the tenth vertebra was a very vascular mass. It was friable.



Small fragments only could be obtained with a curette, which seemed to fall into a cavity lateral to the spine. The wall of the cyst was reported as arachnoid tissue, the curettings of the other tumor as neuro(sympatico)blastoma.

The first spinal puncture done after the operation showed that the block persisted. In view of the character of the tumor radiotherapy was given, and subsequent manometric



FIG. 1. The bone lesions at the eighth and the tenth thoracic vertebrae.

studies showed no block. The only change in the physical signs, however, was a lowering of the sensory level to the twelfth thoracic dermatome. The original sensory level was due to the arachnoid cyst, the lower level corresponded to the site of the lower tumor.

#### COMMENTS

It is impossible to state whether the tumor was a primary one extending into the canal from the adjacent adrenal structure or whether it represented a



metastasis. Against the latter was the lack of evidence of any other lesion clinically or by x-ray examination of the chest.

In a recent report of a spinal extradural arachnoid cyst Good, Adson and Abbot (1) give the total of such cases including theirs as 21. They call attention to the fact that the majority of such cysts have been found in the adolescent group. Of the 21 cases only three were over 26 years of age. In a report in 1934 Elsberg, Dyke and Brewer (3) first called attention to this type of lesion in adolescents. They postulated that the cysts are due to a congenital diverticulum of the dura mater or to herniation of the arachnoid through a congenital defect. In support of this they point out that the opening is near the dural opening for a nerve root. In the case reported here the attachment was near the mid line as it was in the case reported by Mayfield and Grantham (4).

#### SUMMARY

A case is reported which had at the tenth thoracic vertebra an extradural neuro(sympatico)blastoma and at the eighth thoracic vertebra an extradural arachnoid cyst. The latter is an unusual intraspinal lesion, especially infrequent in adults.

#### REFERENCES

1. GOOD, C. A., ADSON, A. W., AND ABBOT, K. H.: *Am. J. Roentgenol.*, 52: 56, 1944.
2. EHNI, G. J.: *Proc. Staff Meetings Mayo Clinic*, 19: 489, 1944.
3. ELSBERG, C. A., DYKE, C. G., AND BREWER, E. D.: *Bull. Neurol. Inst., New York*, 3, 395, 1934.
4. MAYFIELD, F. H., AND GRANTHAM, E. G.: *Surgery*, 11: 589, 1942.

## THE SURGERY OF GASTRIC, DUODENAL AND JEJUNAL ULCER<sup>1</sup>

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The concept is gradually being recognized that gastro-duodenal ulceration is a recurrent disease which in many cases is psychosomatic in origin. It has for its basis an emotional instability, aided and abetted by aggravating environmental factors and influenced in part by seasonal variations. The increased secretion of acid, a potent factor in the production of ulcer, is probably the result of these concomitant factors, but not the primary cause, for there are innumerable patients who suffer from definite hyperacidity yet never develop an ulcer. If the therapy of ulcer is to be ultimately placed upon a more rational basis, then its treatment should not consist of diet and anacids alone. Any qualified physician can prescribe a proper diet such as that of Sippy, and institute the effective milk and aluminogel drip (Winkelstein and his associates (1, 2)) which will temporarily heal an ulcer, but the permanent cure of the ulcer diathesis has deeper implications. It still presents an unanswered challenge to the internist, gastro-enterologist and psychotherapist.

In its inception, ulcer of the stomach and duodenum is certainly not a surgical disease. It only becomes one when certain complications ensue which may threaten the life of an individual. The indications for surgery have been definitely crystallized. Gastric ulcer becomes a surgical emergency when an acute perforation occurs. It ultimately becomes a surgical problem when hemorrhages are recurrent, when a pyloric stenosis becomes intractable, when the symptomatology fails to respond to medical therapy, and when the presence of a carcinoma is suspected. The differentiation between a benign and malignant ulcer may offer difficulties, and presents a pertinent problem in all gastric ulcers. The presence of free hydrochloric acid in a Rehfus test meal does not eliminate the possibility of a new growth. The fact that an ulcer grows smaller or seemingly disappears following three weeks of medical treatment, as evidenced by the roentgen examinations, cannot be construed to mean that a carcinoma is necessarily absent. While gastroscopic examination has been of inestimable value in reducing the incidence of this diagnostic error, its worth is directly proportionate to the skill and experience of the gastroscopist in the interpretation of the pathologic picture which presents itself. Besides, there are areas in the stomach which the flexible Schindler gastroscope cannot visualize. We have removed a few gastric ulcers which, according to all gross pathologic criteria were considered to be benign, but which were proven to be malignant by subsequent microscopic examination. It is true that a benign ulcer rarely undergoes malignant transformation, but according to Klein (8) it did occur in two instances in a series of one hundred and forty-one chronic gastric ulcers, and recently Yarnis and Colp have had occasion to report three cases of benign ulcer in association with an independent gastric carcinoma. If all these factors were born in mind, there

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would be less hesitancy on the part of the medical profession in subjecting recurrent gastric ulcers to radical surgery.

The indications for surgery in duodenal ulcer are similar to those in gastric ulcer except that the question of malignancy rarely enters into this clinical picture. Duodenal ulcers, in addition to acute perforations which constitute an emergency, come within the province of surgery when repeated medical cures have failed to relieve the symptomatology, when hemorrhages are recurrent, and when an intractable duodenal stenosis or pyloric obstruction exists.

Many of the advances in the surgery of peptic ulcer are those which have followed the progress of surgery in general. Specific advances in the surgical treatment of peptic ulcer comprise those operative procedures which have been developed in order to attack the ulcer problem on a more physiologic basis.

If the morbidity and mortality of major surgery in gastroduodenal ulcer are to be kept within reasonable limits, certain ante-operative prerequisites must be carefully followed. Many of the patients who are admitted to the surgical ward service of any large metropolitan hospital have suffered for years from the devitalizing effects of recurrent chronic ulceration. These patients as a rule have lived upon a poorly balanced diet, deficient in vitamins and poor in nutritional content. Bouts of persistent vomiting incident to pylorospasm, pyloric or duodenal stenosis invariably produce inanition, dehydration, avitaminosis, hypoproteinemia, and occasionally alkalosis. The persistent oozing and seeping of blood from a mucous erosion or the crater of a chronically infected ulcer may produce a marked and chronic anemia with all its implications. All these physical alterations and chemical imbalances, unless carefully and accurately corrected prior to operation, militate against successful major surgery.

We feel quite strongly that the chronic complications of peptic ulcer, especially hemorrhage, should rarely be considered a surgical emergency. We do not subscribe to the dictum of a Viennese surgeon who advocated operation within the first forty-eight hours in patients over forty-five years of age who were suffering from a massive hemorrhage. If this dictum were universally followed, the surgical mortality would transcend the wildest estimates, even if these patients received intensive preoperative preparation. Undoubtedly the administration of blood and plasma may effectively and temporarily increase the number of red blood cells, raise the hemoglobin, elevate the blood pressure and theoretically eliminate shock, but the impoverished tissues of the body are slow to recuperate from the dire effects of a pre-existing anoxemia. As a result, a dehiscence of the intestinal suture line and pulmonary complications are frequent. We agree with Crohn and Lerner (7) that the best results in bleeding ulcer will be attained by conservative medical treatment along the lines suggested by Muelengracht, deferring operation until these patients have fully recovered from the effects of their blood loss.

Prior to operation most patients suffering from chronic peptic ulcer require adequate hydration and restoration of the electrolytic imbalances by the parenteral administration of glucose and saline. Hypoproteinemia, if present, may be corrected by the oral administration of a high protein diet. If this is

impractical because of vomiting, the intravenous use of blood plasma and amino acids may effectively elevate the lowered serum proteins. But patients suffering from the effects of pyloric stenosis require additional preparation. Daily hot gastric lavages usually relieve pylorospasm and often allay the local inflammatory reaction to such a degree that gastroduodenal continuity will be restored, and the accompanying alkalosis will usually respond to intravenous saline in adequate amounts. If, in spite of these measures, the gastric dilatation persists and the alkalosis becomes increasingly severe, a preliminary jejunostomy for alimentation may become necessary. The indications for jejunostomy which have proven to be so invaluable in the surgery of gastroduodenal ulceration (6) will be briefly discussed subsequently.

After a patient has been adequately prepared for operation, the question of anesthesia arises. All types and combinations of inhalation and local anesthetics have been employed during the past decade. In our experience, continuous spinal anesthesia with *pontocaine* has proven to be the most satisfactory in the surgery of the upper abdomen. This method permits a minimal dose of the anesthetic agent to be primarily injected and if additional anesthesia is required more of the drug may be introduced through the lumbar puncture needle which remains in place through the operation. However, if the patient is unduly apprehensive, sodium pentothal may be used intravenously.

The abdomen is usually explored through a median epigastric incision extending from the ensiform to the umbilicus. At the present time there seems to be almost universal agreement as far as the surgery of gastric ulcer is concerned. The local excision of the ulcer with or without gastroenterostomy, and a sleeve resection in which a segment of the stomach bearing the ulcer was removed, have been definitely discarded because in many cases the patients were unimproved. Often, in spite of gastroenterostomy, the gastric ulcer recurred or a gastrojejunal ulcer developed, and frequently following sleeve resections an hour glass deformity of the stomach ensued. In most clinics these antiquated procedures have been replaced by a partial or subtotal gastrectomy, an operation in which the pylorus and the ulcer bearing area of the stomach are removed. Gastrointestinal continuity is then restored by a Billroth II type of anastomosis, or one of its modifications.

The follow-up results following subtotal gastrectomy for gastric ulcer have been excellent. This operation is invariably accompanied by a gastric anacidity and, in our experience, recurrent gastric, duodenal or gastrojejunal ulcer rarely occurs when free acid is absent. However, the objections to the operation have mainly centered about its mortality. In a presentation before the New York Surgical Society, February 26, 1936, Klingenstein (9) presented a series of gastric ulcers, from 1925 to 1935, in which a subtotal gastrectomy was done. The mortality was appreciable. He predicated at that time that if operations in the bleeding stage were eliminated and resections were not done for ulcer in the cardiac portion of the stomach, the mortality would be materially lessened.

In the past six years, in a series of consecutive gastric ulcers in which a subtotal gastrectomy was the only operation employed, the mortality was distinctly

reduced. However, only one of the patients was operated upon during an acute episode of hemorrhage and in five cases in which the ulcer was juxta-esophageal, a palliative gastrectomy was performed. This was an operation devised by Madlener (10, 11) in 1923 for ulcers which were proximal to the re-entrant angle, especially in the poor risk patient. In this procedure a pylor-ectomy was performed leaving the ulcer *in situ*. Subsequently, Flörcken (12, 13) and others (14, 15) resected as much of the antrum as was possible. These observers reported that the gastric ulcer which had not been removed, eventually disappeared according to roentgen examinations, and that the patients were relieved clinically. Four patients in whom a palliative gastric resection was done have remained well. Gastroscopy and roentgen examinations have failed to demonstrate any recurrence. A sufficient period has elapsed following operation so that the disappearance of the ulcers could not have been attributed to a natural spontaneous regression which may occur during the life cycle of an ulcer. We feel that the resultant anacidity in these cases protected the integrity of the gastric mucosa.

While the operation of gastric resection for gastric ulcer has been accepted by most surgeons as the procedure of choice, there is no unanimity of opinion as to the surgical treatment of duodenal ulcer. The operation of subtotal gastrectomy for duodenal ulcer was originally advocated by Von Haberer in 1920. It was introduced by Berg (3) and Lewisohn (4) at the Mount Sinai Hospital in 1922, and through their pioneering efforts this procedure has gradually gained in popularity in this country. It is now being extensively used in clinics which many years ago denounced the procedure as unnecessary because it was their considered opinion that a simple gastroenterostomy had been effective in relieving the symptoms in the majority of their patients. But gastroenterostomy with or without removal of the duodenal ulcer, and the various plastic procedures which were performed after the ulcer on the anterior wall was excised, did not produce such excellent follow-up results when patients were carefully followed for years and questioned in personal interviews. In many the symptoms were unrelieved. Pylorospasm continued, hemorrhages recurred, and unfortunately a few were made worse by the operation of gastroenterostomy because a gastrojejun- al ulcer developed. Gastrojejunal ulceration may cause agonizing pain, persistent vomiting, severe exsanguinating hemorrhages, and often perforations into the general peritoneal cavity or into the transverse colon. The incidence of this untoward complication following gastroenterostomy has been reported as high as 50 per cent in some series of cases. Its etiology is not definitely known, but many gastrojejunal ulcers seem to develop in the presence of a persistent high free total acid in patients who have an innate tendency to develop ulcer. Clinically, the operation of subtotal gastrectomy which partially eliminates the humoral phase of gastric secretion, causes a definitive lowering of gastric acidity in most instances, and produces an anacidity in 50 per cent of the cases. For the reason that a gastric anacidity is protection against further development of recurrent ulceration, and the fact that most patients are definitely relieved of their symptoms, the operation of subtotal gastrectomy continues to be the



operation of choice in this clinic. However, it cannot be done in all cases, and is contra-indicated in the poor risk patients, those with obesity, hypertension, severe myocarditis or diabetes. In these patients a simple gastroenterostomy must suffice in spite of its unfavorable complications.

Subtotal gastrectomy is a complicated technical procedure and requires specialized experience. The real hazard of the operation centers mainly about the adequate closure of the transected duodenum which often may prove to be extremely difficult if the ulcer is extensive, if the tissues are brawny and indurated, or if the ulcer is deep in the duodenum. But there is no reason to remove an ulcer if certain technical difficulties are present. I have never felt that its removal was an essential part of the operation of subtotal gastrectomy as long as the entire pylorus and antrum were resected. In the final analysis, the operation of subtotal gastrectomy of the Billroth II type diverts the gastric contents and puts the duodenum at rest so that any ulcer which has been left *in situ* bathed by the alkaline secretions of pancreatic juice will ultimately heal. These clinical impressions were further confirmed by the observation of Mage (5) who reported that gastrojejunal recurrence following subtotal gastrectomy for duodenal ulcers were not greater in those cases in which the ulcer had not been radically removed. However, if the danger of a subtotal gastrectomy centers mainly about the integrity of the duodenal suture line, then drainage should be instituted. This does not always protect against the ravages of a spreading peritonitis from a dehiscence of a duodenal stump but it has proven invaluable in directing the external escape of duodenal contents in most cases. Duodenal fistulae no longer portend such dire consequences for the immediate institution of suction protects the surrounding skin against the ravages of activated intestinal secretions and adequate parenteral therapy is usually effective in combatting dehydration and chemical imbalances. If life is threatened because of a complete loss of fluid, food, bile and pancreatic secretions, a supplementary jejunostomy for alimentation makes possible the maintenance of nutrition and the return of the aspirated duodenal contents. Jejunal alimentation, together with parenteral therapy if necessary, will maintain a patient in chemical balance and nutrition until the duodenal fistula heals spontaneously.

Certain other advances have been made in the technique of gastric resection. The rubber covered clamps which were applied prior to transection of the stomach have been discarded in favor of the DePetz sewing instrument which lays down a double row of clips through which the stomach may be divided. This machine is usually applied proximal to the re-entrant angle so that an adequate portion of the stomach may be resected. Gastro-intestinal continuity is then usually restored by a termino-lateral gastrojejunostomy of the Hofmeister type. The anastomosis is now made anterior instead of posterior to the colon. The antecolic anastomosis undoubtedly simplifies the operative procedure, and should a gastrojejunal ulcer develop, its excision would entail no risk of injury to the middle colic artery. In addition, no differences were noted in the immediate postoperative course and follow-up results of either the ante- or retrocolic types of termino-lateral gastrojejunostomy. During the past six years, subtotal



gastrectomy was performed for duodenal ulcer in one hundred and sixty-three ward patients. The results were recently published (16). The cases were divided into two series—series A, 79 patients, from July 1, 1937 to June 30, 1940, and series B, 94 patients, from July 1, 1940 to June 30, 1943. A study of Table

TABLE I  
*Analysis of deaths in subgroups*  
Series A

|  | NO. OF<br>CASES | NO. OF<br>DEATHS | CAUSE OF DEATH  | MOR-<br>TALITY<br>RATE<br><br>% |
|--|-----------------|------------------|---|---------------------------------|
| Duodenal ulcer.....                          | 48              | 3                | (1) Cerebral thrombosis<br>(2) Generalized peritonitis<br>(3) Alkalosis   | 6.25                            |
| Bleeding duodenal ulcer.....                 | 16              | 3                | (1) Duodenal dehiscence<br>Generalized peritonitis<br>(2) Hemorrhagic bronchopneu-<br>monia<br>(3) Subphrenic and subhepatic<br>abscesses | 18.75                           |
| Previously perforated duodenal<br>ulcer..... | 15              | 2                | (1) Massive atelectasis<br>(2) Pneumonia after drainage<br>of subphrenic abscess  | 13.33                           |
| Total.....                                   | 79              | 8                |   | 10.13                           |

TABLE II  
*Analysis of deaths in subgroups*  
Series B

|  | NO. OF<br>CASES | NO. OF<br>DEATHS | CAUSE OF DEATH  | MOR-<br>TALITY<br>RATE<br><br>% |
|--|-----------------|------------------|---|---------------------------------|
| Duodenal ulcer.....                          | 67              | 3                | (1) Hepatitis and pneumonia<br>(2) Pulmonary embolism<br>(3) Diffuse bronchopneumonia | 4.48                            |
| Bleeding duodenal ulcer.....                 | 16              | 1                | (1) Duodenal dehiscence<br>(2) Subhepatic abscess                                     | 6.25                            |
| Previously perforated duodenal<br>ulcer..... | 11              | 0                |   | 0                               |
| Total.....                                   | 94              | 4                |   | 4.26                            |

I and II shows that the mortality of Series B is lower than Series A. This improvement might be ascribed in part to the increased skill of the operators, to certain changes which were made in surgical technique, and to the curtailment of surgery in the acute phase of duodenal bleeding (Table III).

It was stated previously that the indications of jejunostomy for alimentation could be briefly discussed. Jejunostomy was employed as a preliminary procedure in a few intractable cases of pyloric and duodenal stenosis, in which gastric dilatation and alkalosis were unrelieved by medical measures. Inasmuch as major gastric surgery was definitely contra-indicated in this type of high intestinal obstruction, a simple jejunostomy for alimentation was performed under local anesthesia. Jejunal feedings of the Scott Ivy pabulum invariably restored nutrition and hydration, and corrected the alkalosis within a short period of time. In addition, the atonic stomach now partially defunctionalized by the elimination of gastric digestion soon regained its tone. Simultaneously the local inflammatory reaction about an extensive penetrating duodenal ulcer subsided sufficiently so that a subtotal gastrectomy could eventually be safely performed without undue risk.

Complementary jejunostomy, a procedure carried out at the same time as a subtotal gastrectomy, was performed with the hope that the procedure might

TABLE III  
*Comparison of the statistics in series A and B*

|   | SERIES A<br>JULY 1, 1937 TO<br>JUNE 30, 1940 | SERIES B<br>JULY 1, 1940 TO<br>JUNE 30, 1943 |
|---|--|--|
| No. of cases.....                         | 79   | 94   |
| Mortality.....                            | 8  | 4  |
| Mortality percentage.....                 | 10.13  | 4.26   |
| Drainage of duodenal stump.....           | 29   | 72   |
| Antecolic type of gastrojejunostomy.....  | 35   | 91   |
| Retrocolic type of gastrojejunostomy..... | 44   | 3  |
| Jejunostomy.....                          | 4  | 32   |
| Spinal anesthesia.....                    | 16   | 84   |
| General anesthesia.....                   | 63   | 10   |

neutralize the deleterious effects often caused by difficulties in gastric emptying. Postoperative gastric atony in our experience occurred quite frequently and in one instance was the cause of death. The mechanisms involved in the pathologic physiology of atony of the resected stomach are not all known. Acute gastric dilatation may be secondary to mechanical factors, such as an occluding edema of the gastro-enteric stoma which is often inflammatory at first, and subsequently is abetted by the biochemical disturbances incident to hypoproteinemia. Occasionally an acute obstruction may develop in a retrocolic gastroenterostomy because of the prolapse of the stoma or the efferent loop into the lesser omental sac. In a few cases the postoperative development of plastic exudate and adhesions may be sufficient to occlude either the afferent or efferent jejunum producing a high intestinal obstruction. But there are cases of acute gastric dilatation or atony in which neither subsequent operative exploration nor post mortem examination reveals any anatomic cause for the clinical symptomatology of obstruction. This type of gastric ileus has been attributed to muscular paresis and atony, the sequellae of unavoidable surgical trauma and injury to the vagus

nerve. It is a common experience, following a simple gastroenterostomy or a gastric resection that twenty-four to forty-eight hours may elapse before peristaltic activity is partially established. The resulting stagnation of accumulated gastric contents and blood either causes repeated vomiting or persistent gastric drainage through an indwelling Levine tube. In the majority of the patients these difficulties in gastric emptying are transient and inconsequential. If they persist they portend serious consequences. It is the systemic effects produced by gastric atony in its varying severity and duration which adds to the morbidity of gastric surgery. It was in those gastric and duodenal ulcers which were complicated by a prior stenosis and gastric dilatation that complementary jejunostomy proved its worth during the early postoperative period. It proved especially helpful in many instances in which gastric atony occurred following unusual traumatic and complicated procedures, as in extensive resections for gastrojejunal ulcers or those ulcers situated in the cardiac portion of the stomach. It is undoubtedly true that complementary jejunostomy was unnecessary in some cases as judged by the subsequent uneventful postoperative course, but even in these patients it did no harm, and certainly simplified postoperative alimentation and curtailed the period of parenteral therapy. Naturally there were cases in which a postoperative gastric atony developed and in which a complementary jejunostomy had not been performed. In these patients a severe gastric atony may occur from the very beginning, while in others it may not be evident until a week or so after operation. The clinical picture, however, is similar in both groups of patients. It is recognized by the symptoms and physical findings of a high intestinal obstruction in which progressive deterioration occurs in spite of adequate parenteral treatment. X-ray examination often discloses a dilated stomach in which the barium is completely retained and occasionally an obstruction of the efferent jejunal loop may be demonstrated. There is always a tendency in these cases to be conservative, to delay operative intervention until it is often too late. This is undoubtedly the reason that the results of secondary procedures in these cases are attended by such a prohibitive mortality. We agree with the conclusions of Allen and Welch (17) that in the older age group of patients, exploration should be undertaken early if the amounts obtained by gastric aspiration show a stationary or progressive increase and the chemical evidences of a marked alkalosis are present. In the younger patients, conservative measures may be tried for a longer period of time. If exploration is performed, a supplementary jejunostomy for alimentation which may be speedily performed will usually tide the patient over the critical period of gastric ileus.

We have already stated that one of the late complications of gastroenterostomy is the frequent development of a gastrojejunal ulcer. Unfortunately, however, it may occasionally occur following a subtotal gastrectomy for duodenal ulcer. Mage followed five hundred and two patients in whom a subtotal gastrectomy had been performed for duodenal ulcer for varying periods from 1923 to 1940. Clinical evidences of gastrojejunal ulceration were noted in forty-one cases. The diagnosis was definitely established by operation or by autopsy in thirteen cases.

Gastrojejunal ulcer is always a serious complication and the therapeutic approach to the problem demands an intimate knowledge of the pathology and pathologic physiology induced by these lesions (18). It is important to know the extent, character, and location of the ulceration. Some jejunal and marginal ulcers may erode blood vessels, producing severe hemorrhage, or perforate either into the free peritoneal cavity or into the colon, causing a gastro-jejuno-colic fistula. Other slowly penetrating ulcers may be effectively walled off either by the transverse mesocolon, colon, pancreas or intestines, resulting in a large intraperitoneal inflammatory exudate. Occasionally the inflammatory reaction may be so extensive that either an acute or subacute obstruction of the gastroenteric stoma or the efferent loop may result. This acute inflammation may eventually subside completely, or leave within its wake some degree of obstruction. Obstruction of the gastroenteric stoma, especially if accompanied by a pylorospasm or duodenal stenosis, produces a dilatation of the stomach. The resulting inability to retain food, and the loss of gastric secretions lead to those nutritional disturbances which have been previously described.

All patients with gastrojejunal ulceration should receive a course of medical treatment, if not permanently, at least temporarily. However, when medical treatment becomes ineffectual, or the economic condition of the patient is such that the pattern of life cannot be made to conform with the routine prescribed, or if acute symptoms of jejunal perforation become manifest, surgery is indicated. The type of procedure indicated in cases of gastrojejunal ulcer depends upon the existing pathology and the physical condition of the patient. Past experiences have taught us that if better and more satisfactory follow-up results are to be expected, certain operations must be discarded. Simple excision of marginal ulcers of the stomach and jejunum with some type of plastic repair has proven to be ineffectual. The addition of a new gastroenterostomy in addition to the one which contains the ulcer, or the separation of the old gastroenterostomy and the formation of a new stoma are of little permanent value when there is a tendency for recurrent ulceration. Taking down the old gastroenteric stoma with the excision of the jejunal ulcer as a definitive procedure in the treatment of gastrojejunal ulceration has proved to be unsatisfactory in most cases. The restoration of a normal anatomy is invariably followed by re-activation of the duodenal ulcer, or the possible development of a gastric ulcer. However, under certain circumstances these palliative procedures may be necessary, and may effect sufficient physical improvement so that radical surgery may be eventually performed. The ideal treatment of a gastrojejunal ulcer following gastroenterostomy is a resection of the diseased jejunum and a subtotal gastrectomy of the Billroth II type. If this operation results in a gastric anacidity or the presence of low acid values there is little likelihood of subsequent stomal or gastric ulceration. However, if a gastrojejunal ulcer should develop following a gastric resection it may be necessary to excise more of the stomach, but it must always be remembered that there are individuals in whom nothing short of a total gastrectomy will prevent recurrence.

## REFERENCES

1. WINKELSTEIN, A., CORNELL, A., AND HOLLANDER, F.: Intragastic drip therapy for peptic ulcer. *J. A. M. A.*, 120: 743, 1942.
2. CORNELL, A., HOLLANDER, F., AND WINKELSTEIN, A.: The efficacy of the drip method in the reduction of gastric acidity. *Am. J. Digest. Dis. & Nutrition*, 9: 332, 1942.
3. BERG, A. A.: The mortality and late results of subtotal gastrectomy for the radical cure of gastric and duodenal ulcers. *Ann. Surg.*, 92: 340, 1930.
4. LEWISOHN, R.: Resection of the stomach for chronic gastric and duodenal ulcer. *Ann. Surg.*, 78: 507, 1923.
5. MAGE, S.: Recurrent ulceration following subtotal gastrectomy in the treatment of gastroduodenal ulcer. *Ann. Surg.*, 116: 729, 1942.
6. COLP, R., AND DRUCKERMAN, L.: The indications for jejunal alimентация in the surgery of peptic ulcer. *Ann. Surg.*, 117: 387, 1943.
7. CROHN, B., AND LERNER, H.: Gross hemorrhage as a complication of peptic ulcer. *Am. J. Digest. Dis. & Nutrition*, 6: 15, 1939.
8. KLEIN, S.: Origin of carcinoma in chronic gastric ulcer. *Arch. Surg.*, 37: 155, 1938.
9. KLINGENSTEIN, P.: Transactions of the New York Surgical Society, February, 1936.
10. MADLENER, M.: Ueber Pylorektomie bei pylorusfernem Magengeschwür. *Zentralbl. f. Chir.*, 50: 1313, 1923.
11. MADLENER, M.: Erfahrungen mit der Pylorektomie als indirekter Ulcusoperation. *Ibid.*, 51: 1896, 1924.
12. FLORCKEN, H.: Wesen und Wirkung der "palliativen Magenresektion" beim nicht resezierbaren Ulcus ventriculi und duodeni. *München. med. Wchnschr.*, 75: 1955, 1928. Refers to work of Madlener, 1923.
13. FLORCKEN, H.: Die palliative Magenresektion beim Ulcus duodeni und ventriculi. *Fortschr. d. Therap.*, 8: 37, 1932.
14. WELLS, C. A.: High gastric ulcer; a suggested operation. *Brit. M. J.*, 1: 778, 1933.
15. WALKER, R. M.: The surgical management of high gastric ulcer. *Brit. M. J.*, 2: 967, 1936.
16. COLP, R., KLINGENSTEIN, P., MAGE, S., AND DRUCKERMAN, L. J.: Subtotal gastrectomy for duodenal ulcer. *Ann. Surg.*, 120: 170, 1944.
17. ALLEN, A. W., AND WELCH, C. E.: Jejunostomy for the relief of malfunctioning gastroenterostomy stoma. *Surgery*, 9: 163, 1941.
18. COLP, R.: Surgical problems in the treatment of gastrojejunal ulceration. *Ann. Surg.*, 114: 543, 1941.



## GASTRO-ENTEROLOGY AT THE MOUNT SINAI HOSPITAL

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This Twentieth Century marks the recognition of gastro-enterology as a subspecialty of both medicine and surgery. In previous years the clinical concepts of ulcer, carcinoma, gall bladder lesions, dysentery, pancreatitis, had been described and established, in the fullness of their mature conception, by able clinicians.

This present century is characterized by the fact that the physiological bases of our modern conception of disease, its biochemical substrata, its radiographic appearance, and the proper medical and surgical approach to its cure, have been succinctly elucidated and finally established.

The logical bases, the scientific explanation of the biology of most of these pathological processes have been laid down by great pioneers, many of them American, Pavlow, Cannon, Ivy, Carlson, Meltzer, Babkin, Alvarez in physiology; Holzkecht, Cole, Haudek, Barclay, Graham, in roentgenology; Hurst, Bargaen, Eusterman, Sippy, Thomas R. Brown, Rehfuß, Bensaude in clinical medicine; the Mayos, Von Haberer, Finsterer, Finney, in surgery. These are some of the great leaders who have forwarded the science and the art of the practice of gastro-enterology since the opening years of this eventful century.

Today gastro-enterology as a subspecialty of medicine (and too of surgery) has arrived at years of maturity and of recognition. National and International societies foster the scientific propagation of its development; the American Board of Internal Medicine recognizes a "subspecialty of gastro-enterology" as does the American Medical Association in its annual conclaves. The armed forces of this and other countries recognize the gastro-enterologist in his specialized sphere of activity; and aptly so, for a very considerable percentage of the whole number of morbid and disabled soldiers and sailors suffer from gastro-intestinal derangements "organic" or functional.

Out-patient departments and clinics in large numbers, associated with general hospitals in this country, and many of the largest and most progressive hospitals and institutions recognize special medical and surgical services for the study and care of disease arising in the alimentary tract and its associated viscera.

The Mount Sinai Hospital, true to its reputation for the quick recognition and appreciation of progress in the various fields of medicine has been no laggard in respect to gastro-enterology, in fact, in many aspects and ways it has contributed its full mead and share in the scientific advancement of this specialized field. In the early years of the century, Lilienthal and Gerster strode the surgical wards of the hospital interested impartially in all phases of scientific surgery. The high-sounding Gerster, (often irritated by gout), always fair and just, masking a kindly and true soul under an autocratic manner; the benevolent and lovable Lilienthal, ingenious, resourceful, capable, were interested alike and evenly in all the surgical problems of the day.

In 1914 this dynasty fell on the shoulders of four very competent men who,



truly representative of progress coincident with the changing times, soon developed specialized spheres of activity and influence. Charles Elsberg was early recognized in neuro-surgery; Edwin A. Beer in genito-urinary diseases, A. V. Moschcowitz for his meticulous care and infinite patience with the repair of hernia. To Albert A. Berg surgery of the alimentary tract had always been an item of extreme interest, not alone for practice in surgery but for the statistical study of the end-results and the physiological bases of its associated diseases. To the Surgical Service of Dr. Berg were assigned the twenty-five beds reserved for operations upon the alimentary tract.

The foundation of the "Wimpheimer Ward for the Surgical Treatment of Diseases of the Stomach and the Intestines," made possible by the generous gift of Mr. Charles A. Wimpheimer in 1917 gave a remarkable stimulus to the work in this broad field. It allowed for the segregation of similar cases, for their organized study, their statistical evaluation, and encouraged research in the physiological and biochemical supporting sciences. The old Ward M on the ground floor of the previous Children's Pavilion became a rallying point for many interests. Here were seen for the first time, groups of identical type patients, gastro-enterostomies for ulcer, cholecystectomies, colectomies, intestinal tract sutures and anastomoses. Ably cooperating were his associates, Doctor Richard Lewisohn, followed by Paul W. Aschner (1929) and Sunday mornings "Grand Rounds," found not only the full surgical staff and visitors but also the generous, the able, the practical clinician Dr. Edward A. Aronson and his staff from the Gastro-intestinal Division of the Out-patient Department.

For soon after the foundation of the specialized surgical wards for gastro-enterology, the need and advisability of medical cooperation became apparent to the head of the Surgical Service. The first recognition of medical gastro-enterology in the hospital dates from the inception of a specialized out-patient division for this purpose. The organizational leadership fell, and rightly so to Dr. Edward A. Aronson who on the Fourth Floor of the Clinic on Madison Avenue established in 1913 this specialized subdivision of medicine which, soon gathering momentum, outgrew its rooms, increased its personnel, and shortly became one of the fastest growing and popular and well organized subdivisions of that teeming hive of activity, the Out-patient Department.

Grand Rounds under Berg on a Sunday morning were a source of instruction and of pleasure. Begun at 9:30 promptly, the large caravan of Surgical and Medical associates, the House Staff, nurses and visitors made the rounds from bed to bed. Discussion was open, full and unlimited, opinions were ventured without restraint, the lowliest could be heard from. The discussion ranged over problems of diagnosis, of surgical technic, of medical indications, of physiological explanation of phenomena. Careful statistics were mandatory and the subsequent follow-up of previously operated cases was a feature of the greatest care and solicitude. The Rounds would continue for hours with unceasing interest until the clatter of dishes and carts announced the advent of the noon-day meal. But not even that diversion could quell the scientific interest of those who attended. The morning was frequently capped-off with the view of a visitor, a former pa-

tient who had survived for years the operation (rare in those years) of total gastrectomy for carcinoma of the stomach who demonstrated his full return to health by finishing off a full meal to the delectation of Dr. Berg and his associates.

On the medical side of the house gastro-enterology made a more tardy beginning. While still a house physician this author served under the bearded and kindly Dr. Julius Rudisch whose main interest in medicine centered upon diabetes mellitus, its control and the study of acidosis as a complication. Everyone who came under the influence of this generous man, had to earn his way to good will by working on the problem of quantitative acetone determination in the diabetic urine. Dr. Herbert Celler had tried it before me, and gleefully passed on the problem to my amateur hands. It was easy to add some sodium nitroprusside to urine and develop a reddish-brown coloration, but to standardize the technic, to develop a control color-standard presented in those pre-colorimeter days, an imposing problem. During the discussion, one day, of the difficulties of the problem a visitor was announced, none less than the illustrious Dr. Max Einhorn of the German (later Lenox Hill) Hospital. Dr. Einhorn was a colleague and friend of Dr. Rudisch and his entry on rounds on Ward K brought to that ward a breath of gastro-enterology associated with a scientist and clinician of renown, known the world over for his inventiveness and ingenuity and his interest in gastric and pancreatic problems. Dr. Einhorn carried with him a new toy he had devised, a duodenal bucket on a string. The bucket would be swallowed by the patient until it had reached the duodenum, whereupon it was retrieved by means of the string, the bucket containing golden pancreatic juice for quantitative analysis. But in addition, Dr. Einhorn arrived with a new long flexible rubber tube or catheter which could be swallowed or passed through the pylorus into the duodenum; and which, when aspirated, brought forth duodenal and mixed pancreatic juice for study and analysis. I presume Dr. Rudisch interrupted his discourse on diabetes long enough to show a polite interest in his visitor's delectable pancreatic problems, sufficient to inspire Dr. Einhorn to leave both gadgets with him as a present and a mark of lifelong friendship. When Einhorn had been politely escorted to the door with the salutary farewell, Dr. Rudisch turned to me and handing both trinkets to me said, "Here young man, these may interest you—play with them."

Thus began, in a small way, the early studies on pancreatic enzymes and function in the medical wards of the hospital. Soon after, in 1915, a very similar catheter for the study of gastric secretion was devised by Dr. Martin Rehffuss of Philadelphia, and his series of publications on fractional test meals of the stomach soon replaced the older Ewald, Boas, Riegel, Leube test meals in interest and in worth and value. Under the kindly advice and aegis of Dr. Sam Bookman, Bio-chemist to the hospital, the studies in Mount Sinai on test meals, fractionation, on the effects of pharmaceutical agents on gastric secretion, on variations in secretory curves in health and disease took a rapid step forward, as did the studies on pancreatic secretion and functional activities.

The early and untimely death of Dr. Edward A. Aronson (1922) less than nine years after he had founded the Gastro-enterological Clinic in the Out-patient

Department was a source of great sorrow. His office and mantle fell upon myself; ably assisted by the newly arrived Dr. A. Winkelstein, as well as by Dr. Samuel J. Goldfarb (then an amateur radiologist) by Paul Aschner, Ed Hollander, Samuel Weiskopf and many others, the clinic grew to importance and to recognition as a consultative center for the O.P.D. and as a focal point for problems gastro-enterological.

*Sub-total Gastrectomy.* During the first two decades of this century the operation of gastro-enterostomy was regarded as the cure for all gastric diseases, not only for ulcer, but often for functional disturbances as well. It must be remembered that the roentgenographic diagnosis of gastric disorders was developed in accuracy and precision only later in the second decade, that the direct recognition of duodenal ulcer was in like manner stimulated by the work of Lewis Gregory Cole, of Ackerlund and of Clairmont. Most all diagnoses were tentative; any clinical suspicion of carcinoma must be resolved by the only certain method namely exploratory laparotomy. Once an abdomen was opened for gastric symptoms, either a resection for suspected malignancy was performed or else a gastro-enterostomy and if no lesion was found, a gastro-enterostomy was often performed since supposedly it could do no harm and even a functional disturbance could be improved by so simple a drainage procedure as a new stoma between stomach and intestine.

But soon the weather thickened, some fogs of doubt began to cloud over the unstained reputation of gastro-enterostomy. It was whispered that gastro-jejunal ulcers were not infrequent, but that of course, was heresy. For from above, from the Western authorities and from the country at large came, obiter dictum, that 2 per cent was the upper limit of incidence, if that much. But the murmurs of discontent and doubt were rising above hushed whispers, and here and there a hardy pioneer soul dared to state that gastro-enterostomy was a poor operation and that recurrent ulcers were far from infrequent. Later the unfeared voice of "thirty-three per cent" Lewisohn was heard high above the discusional din. What Lewisohn actually said (1925) was that 33 per cent of gastro-jejunosomy operations developed marginal ulcers. What he really reported was that in a series of gastro-enterostomies reviewed by him at the hospital, he found 33 per cent to be suffering with marginal ulceration. In the fury and clamor that followed his publication he was much misquoted and misunderstood. But those who knew him, who realized his great worship of truth, his personal scientific integrity and his zeal for clear unprejudiced thinking, paused long enough to recognize that here was a real challenge to an operative procedure which was outliving its usefulness.

At about this same time, even before it (1917) A. O. Wilensky and myself, by means of kymographic studies and fractional test meals, had been studying the physiological results of this same operation of gastro-enterostomy. Our results led us to doubt that the operation had a sound physiological basis, to question whether acidity was sufficiently reduced and motility proportionately accelerated to warrant the use of the operation in any cases except those of pyloric stenosis. In those years Dr. William J. Mayo of Rochester, Minnesota had been in the

habit of periodically visiting The Mount Sinai Hospital on his travels to this city, his open and frank unprejudiced mind seeking facts and ideas wherever such originated. Instigated by Dr. Libman he sat down for a moment in the old laboratory on Madison Avenue to listen to the results of these studies on the physiology of gastro-enterostomy. As the shadows of the afternoon lengthened, —he tarried long—when he finally departed it was with the startling suggestion that two young men accept an invitation through him, to the American Gastro-enterological Association to demonstrate and present their findings. The rising note of thanks from that national body including S. J. Meltzer, Einhorn, Sippy, Friedenwald, Cannon that May in Atlantic City, did more than embarrass two very young and inexperienced men. It brought attention and I hope credit, to the active interest in gastro-enterology that was gathering momentum at Mount Sinai, and centered interest in the criticism of the accepted operations for gastric disturbances of that day and period.

As was his wont, once again the enquiring Lewisohn crossed the Atlantic in search of rest, recreation and naturally of knowledge. It was summer time and the Bavarian Alps in 1922 were alluring and homelike; *gemuetliches Innsbruck* was not too far south, and there was to be found the surgeon Von Haberer, who had devised a new operation, partial gastrectomy for the cure of peptic ulcer. The return voyage on the *Aquitania* was the stormiest trip in thirty-seven years, but over the howling of the gale, and between the spells of devastating seasickness (to which he was immune) he enthusiastically recounted what he had seen and heard from Von Haberer and waxed enthusiastic over what he considered would eventually become a bright new future for gastro-intestinal surgery, namely the radical removal of a greater part of the stomach itself, as well as the offending ulcer (partial gastrectomy).

Resuming his duties as Associate Surgeon to his Attending Dr. A. A. Berg, he needed little persuasion to convince his senior of the practicability and fitness of the new operation. Like all converts to a new faith, the enthusiasm of Dr. Berg was sincere and wholehearted. The details of the operation were easily mastered by so great a natural technician as Berg, renowned for his skill and deftness. The mortality of the operation at first high, was rapidly reduced to within safe limits. The results of the operation were eminently satisfactory; secretory studies proved that post-operative acidity was abolished in the highest percentage of cases, motility and emptying time of the viscus was increased and was satisfactory. The number of cases which underwent the operation increased apace; within a few years six hundred cases were statistically possible for accurate review. Indefatigable follow-up was the rule and index files were maintained and a whole Social Service was developed to trace each individual who had undergone the new procedure.

But to convince the profession of this large country with its approbation still fixed upon the older procedure, was an entirely different matter. To this purpose, Berg and Lewisohn took the stump as crusaders. They stumped the country with no uncertain step; on one occasion the Massachusetts Medical Society at Springfield, Massachusetts, at another a national Society at Washing-



ton, D. C.; later in 1933 the American Gastro-enterological Association again at Washington, these were all discussional sites of combat where the earnest attempt was repeated and repeated to put over the new operation and to convince the medical and surgical fraternity of its practicality and its relative safeness. Too big an operation for so small an ulcer? No, if it were necessary to remove one third, or even one half of the stomach to cure a gastric or a duodenal ulcer the purpose was well accomplished, providing gastric acidity were abolished. Thus grew again a second motif, an important and resounding corollary fact, namely that the elimination of the acid was the primary objective of the operation, as well as the removal of the ulcer. Slowly the great tide of public medical opinion swung to the new thought. Grudgingly the operation was conceded as choice in "gastric" ulceration. Then little by little it became the procedure of choice for "duodenal" ulcer as well. Throughout the nations the mortality was hammered down; first 14 per cent, then 9 per cent, then 7 per cent, and 5 per cent until recently different clinics report mortalities between two and three per cent. Thus was a campaign in which the The Mount Sinai Hospital was one of the leaders in thought and action brought successfully to fruition—the "Acid School" had won the fight for gastric resection.

In the fullness of his years, Dr. A. A. Berg stepped out of the Ward Service and became Consulting Surgeon continuing to serve the one institution with fidelity and with the ability derived from his wide and mature experience.

Dr. Richard Lewisohn took over, (1934 to 1937) carrying on the principles and practices of progressive gastro-intestinal surgery with scientific accuracy, always honestly facing his after-results and always hailed by a large coterie of personal friends in the profession who valued his opinion and his frank and unbiased criticism.

During this period, even before, the position of "Associate-in-Medicine" had been created to recognize the needs of specialization in the medical wards of the hospital. Dr. Nathan Rosenthal represented hematology; I was appointed to represent gastro-enterology (1926). Here was a new type of rank on the attending staff, one that granted privileges of clinical research, one that carried the duty of studying and correlating groups of cases of identical clinical material. The correlation of all proctological examinations naturally followed, as did participation in the recently founded Consultation Clinic (1931) and the privilege of free consultation on the medical wards of the hospital.

The recognition of diseases of the rectum and anus as a surgical subspecialty was indicated by the appointment of Dr. Sylvan Manheim to a Proctological Surgical Clinic (1936) in the expanding Out-Patient-Department.

The affiliation of the hospital with Columbia University (1930) for the purpose of Post-Graduate teaching did much to create greater interest and utility in subjects gastro-intestinal. For from the very initiation of such teaching the courses in gastro-enterology were among the most popular and well attended; in this last year (1943) one Intensive Course alone numbered not less than twenty-four post-graduate practicing physicians. The courses, while specialized, included internal medicine, surgical indications, gastro-intestinal physiology as well as the underlying pathology and bio-chemistry of alimentary disorders.

*The Newer Surgical Services.* Gastro-enterology is easily as much surgical as it is medical. When Doctors Ralph Colp and John Garlock (1937) took over the direction of surgical gastro-enterology, surgical wards and material were eventually divided between these two competent leaders. At first Colp took the intestinal cases (1934 to 1937) Lewisohn continuing with the gastric material. About three years later (1937) a change occurred,—Colp taking the gastric and Garlock taking the intestinal cases. The last eight years have seen a quickened tempo in the handling of gastro-intestinal surgical cases, the newer and younger hands approaching the ever-changing problems with alert vigor and quick recognition of innovations in technique and in operative and post-operative care. As a single example of the mastery of surgical technique and judgment, one may mention the successful removal of carcinoma of the cardia of the stomach through a transthoracic approach as fundamentally conceived and carried out by Dr. John Garlock.

As an indication of the times, of the bold and capable attack on surgical problems one may recall a recent "Grand Rounds" on Ward R. with Dr. Colp when on the one ward one could interview four cases of "total" gastrectomy, simultaneously convalescing from this massive surgical procedure. Wednesday morning "Grand Rounds" beginning at 9:15 and ending promptly at 10:00 a.m. are marked by precise presentation of cases, free and incisive discussion, frank and scientific criticism open to all visitors and well attended.

On the Thursday morning Rounds with Dr. Garlock one may review surgery of the colon and intestine in all its various aspects. Colectomies, sub-total colectomies, intestinal anastomoses of various types, reconstruction surgery for ulcerative colitis, and much of the newer surgical approach to the cure of ileitis, all are available for study.

For in 1932, dated from The Mount Sinai Hospital, appeared the first paper or papers on a new clinical entity "regional ileitis." The earlier pathological and clinical studies on intestinal granulomata had been laid down by Drs. Eli Moschcowitz and A. O. Wilensky as early as 1923. The pathological studies of these granulomata had been re-begun by Drs. Leon Ginzberg and Gordon Oppenheimer. The combination of these studies with the clinical and surgical observations of myself and Dr. A. A. Berg led in 1932 to the formulation of the entity of "ileitis." With practically no hesitation, with little scientific criticism, but with many constructive additions, the medical profession has accepted ileitis, or regional enteritis, as an established clinical concept. The literature today abounds with publications and figures; in ten years hundreds of cases have been recognized, and have been published in the journals of practically all nations throughout the world. The Attending Staff of this hospital have thus been given proper credit for the recognition of a disease, which knows no limited geographical incidence and which provides an ample and new arena for extensive surgical reparative skill and original initiative.

The Milk-Drip treatment of peptic ulcer initiated by Dr. A. Winkelstein (1933) deserves close attention as an ingenious and eminently original and satisfactory medical approach to the care of the increasingly important subject of



peptic ulceration, not only in peace times, but ever so much more so during the period of war.

The establishment of a specific laboratory for Research in Physiological Chemistry, particularly that of the alimentary tract is well marked by the appointment of Dr. Franklin Hollander (1936). Fundamental research in the intricate problems of gastric secretory activity and associated questions has brought large recognition to an indefatigable worker and to the precise, scientific hospital laboratory under his personal supervision; this laboratory will soon be enlarged through the generosity of Dr. A. A. Berg to spheres of still greater utility. Even the most recent development in gastro-enterology, namely gastroscopy, has received notice. Gastroscopy under Dr. Harry Yarnis has grown within the last three years to a sizable activity. It is not unusual on a single morning to see eight or more cases undergo this complicated but very instructive and helpful diagnostic procedure.

Perhaps the part being played by this hospital in the progress of gastro-enterology throughout the nation can be well illustrated by one not insignificant type of fact. The American Gastro-Enterological Association is one of, if not the representative body of scientists representing this specialty in this nation. Before 1917 only Dr. Manges of this staff was a full member; since that date the membership of that association, though limited to 100 Fellows, has included in the course of these last twenty-seven years many members of our staff including, Crohn, Lewisohn, Berg, Winkelstein, Colp, Hollander, Penner (overseas) and Klemperer.

The last quarter of a century in gastro-enterology has been noted among its innumerable great accomplishments, for rapid and progressive strides for the better understanding and recognition of diseases of the alimentary tract. With great modesty we may hold that Mount Sinai, a small institution in itself, just a private hospital, has contributed its proportionate share to such progress. In the beginning it was the spirit, the initiative of Dr. A. A. Berg who developed the interest and who created the staff organization for its progressive development. In the more recent years, all of the Staff, medical, surgical, pathological, biochemical, has served ably and willingly in carrying on the scientific progress in a specialty in which Mount Sinai is well recognized as a fountain source of originality, of mature criticism and as an institution offering a wide and varied clinical material ably studied and segregated.

Our own men overseas are carrying, we know, the reputation of the hospital into the fields of war. The tremendous experience with traumas and wounds of the abdomen, will, when the men happily return, not only reinforce our diminished staff, but will in their homecoming, reunite us again for greater achievements in the reconstructive period of the new universal peace.

# UNILATERAL ADRENAL APOPLEXY<sup>1</sup>

## REPORT OF A CASE

LEO EDELMAN, M.D.

This case of adrenal apoplexy is reported not so much because of its relative infrequency as the fact that it affords an opportunity to call attention to the clinical syndrome of adrenal infarction in adults recently described by Keele and Keele (4) and also, to the clear-cut clinical manifestations of spontaneous perirenal hemorrhage upon the recognition of which the outcome is frequently so dependent.

*History:* B. S. (Adm. #507736), male, aged 61 years, was admitted to the Surgical Service of The Mount Sinai Hospital July 3, 1943 complaining of severe right upper abdominal and loin pain. He had a dull ache in this region for about one week which suddenly became acute six hours before admission, accompanied by nausea and persistent vomiting. He had been a patient on the Medical Service a number of times from November 1940 to May 1943 for chronic pulmonary emphysema, hypertensive cardiovascular disease, repeated attacks of paroxysmal auricular flutter and two attacks of mild congestive failure. His pulmonary symptoms dated back to influenza pneumonia in 1918. He was last hospitalized from May 29-31, 1943 for an attack of paroxysmal auricular flutter. At that time his blood pressure was 200 systolic and 98 diastolic. There was no history of trauma and at no time were there any symptoms referable to the urinary tract.

*Examination:* On admission the patient appeared acutely ill, temperature 99.2°F., the pulse rate, 100, respirations, 26 and the systolic blood pressure 140, the diastolic 88. There was moderate pallor; the skin was moist and cold. The chest was emphysematous and showed dullness and diminished breath sounds over the right lower lobe posteriorly. The heart was slightly enlarged but without evidence of cardiac decompensation. The abdomen was soft, moderately distended, tender on deep pressure over the right upper quadrant. The rectal examination was negative. The admitting physician suspected pulmonary or mesenteric infarction. A hypodermic injection of morphine controlled the pain. When seen a few hours later by a member of the surgical attending staff, he presented a striking pallor, appeared drowsy, and not in spontaneous pain. The blood pressure rose to 180 systolic and 80 diastolic. The abdomen was moderately distended, soft, and on palpation revealed a fixed non-tender mass filling the right upper and lower quadrants. There was no rigidity or muscle spasm. The rectal examination was negative. Vomiting persisted. A retro-peritoneal or intra-abdominal neoplasm was suspected. Abdominal puncture in the left lower quadrant was negative.

*Laboratory Data:* The urine was negative. The hemoglobin was 80 per cent and white blood cell count, 5,200. The Wassermann was known to be negative on his previous admissions, and an additional one taken on this admission was also negative. A flat plate of the abdomen was negative for free air, x-ray opaque calculus, or any evidence of mechanical obstruction. The chest plate showed evidence suggestive of pneumonic infiltration in the right lower lobe with a small amount of fluid in the right pleural cavity. The patient was observed for several days, during which time he ran a low-grade temperature ranging between 98.8°F. and 101°F. The abdominal pain persisted, controlled by an occasional dose of codeine or morphine. The hemoglobin gradually dropped to 63 per cent but the leucocyte count persisted at a low level, 6000 with 71 per cent polymorphonuclear cells.

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<sup>1</sup> From the Urological Service of The Mount Sinai Hospital, New York, N. Y.

The urea nitrogen was 21 mg. per cent. The abdominal mass became more clearly defined, distinctly oval, smooth, fixed, and occupied the right flank. An intravenous pyelogram taken July 9th showed a normal left urinary tract. The right kidney was displaced mesially and downward with incomplete filling of the pelvis and calyces. The right psoas muscle margin was indistinct. A barium enema excluded any intrinsic lesion in the colon. He was seen in consultation by the Urological Service on July 12 at which time the abdominal findings were confirmed. Cystoscopy was negative. A right retrograde pyelogram again showed the mesial and downward displacement of the kidney by a mass above it suggestive

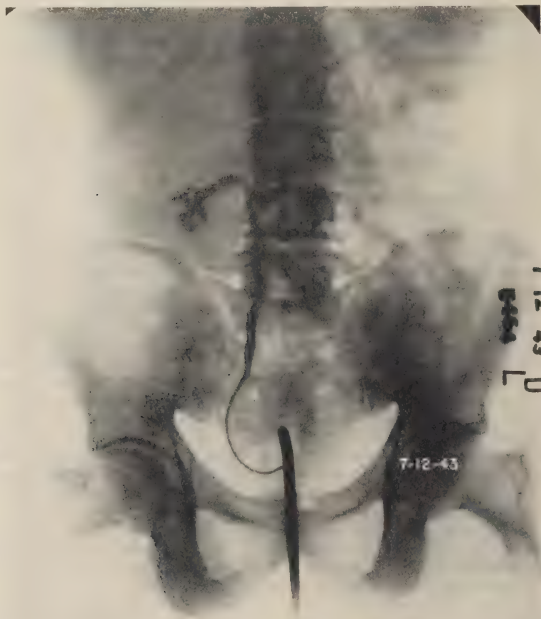


FIG. 1. Retrograde pyelogram showing mesial and downward displacement of the kidney

of upper pole renal or retroperitoneal tumor (fig. 1). On July 16, 1943, under cyclopropane anaesthesia, the right kidney was explored through a typical lumbar oblique incision, including partial resection of the 12th rib. A large, tense, hemorrhagic looking globular mass was exposed, reaching well up under the diaphragm, extending to the mid-line and displacing the kidney downward to the right iliac fossa. It appeared to be intimately connected with the parietal peritoneum and renal capsule. During the process of mobilization, the mass was entered into and about 8 ounces of thick, old blood was liberated. At this stage it was impossible to differentiate between a hemorrhagic lesion of the adrenal or one related to the renal capsule. The kidney, together with the major portion of the

tumor mass including a segment of adherent parietal peritoneum, was removed and the wound closed with drainage.

*Pathological report:* "The specimen consists of resected right kidney with capsule stripped previously and only attached to kidney hilus. The capsule is markedly thickened, measuring up to 2 cm. The pericapsular tissue shows a moderate amount of fat and otherwise is dark red, moderately firm and moist suggesting a hemorrhage. Within this tissue, a portion of adrenal can be seen showing golden yellow cortical tissue. The medulla cannot be made out. The inner surface of the kidney capsule is smooth and bluish red in color. The kidney surface is smooth except for a few flat, irregular depressions measuring up to 0.5 cm. On section, the kidney parenchyma is pale. The ratio is normal. The cortical medullary demarcation is fairly distinct. At a depressed area there is slight atrophy of the cortex due to scarring. The pelvis and calyces are not dilated. The mucosa of the pelvis shows patchy hemorrhages. There is a segment of 5 cm. of ureter which is not dilated and also shows hemorrhages. The large branches of the renal artery show a smooth intima and a slightly thickened wall. The vein is not unusual.

Sections show necrosis of adrenal with massive hemorrhage and early organization into perirenal and retroperitoneal fat tissue. Arterio-sclerosis of adrenal."

*Post-operative Course:* The patient made an uneventful post-operative recovery, leaving the hospital two weeks after operation. At no time was there any evidence of adrenal insufficiency. The blood pressure at time of discharge was 140 systolic and 88 diastolic. A check-up x-ray of the chest showed complete resolution of the pneumonic process. When last seen on November 18, 1944, he was in fairly good physical condition. The blood pressure 168 systolic and 108 diastolic.

#### COMMENT

This case is the second on record at The Mount Sinai Hospital. The first was one observed by Dr. A. Hyman (3). The patient had hypertensive arterio-sclerotic cardio-vascular disease with hemorrhage into the left adrenal.

Hall and Hemken (2) found thrombosis of the adrenal vein the most frequent cause of hemorrhage into the adrenal in adults. It is more likely to occur in persons with chronic heart disease, long-standing tuberculosis or during the course of an acute infectious disease.

According to Arnaud (1) there are three clinical types of adrenal hemorrhage in adults:

1. The peritoneal type with abdominal pain and vomiting;
2. The asthenic type characterized by asthenia alone leading to death;
3. The nervous type in which the patient is found in coma or delirium with only bilateral adrenal hemorrhages discovered at post mortem.

Lavenson (1908) (5) added a type in which sudden death occurs with no ascertainable cause. Bilateral adrenal hemorrhages are found at post mortem.

It is difficult and usually impossible to recognize the existence of an adrenal hematoma during life.

Keele (4), based on a study of the clinical manifestations in his and thirteen other reported cases, listed the following signs and symptoms constituting a syndrome of adrenal infarction in adults:

Abdominal pain, gradual in onset, increasing in severity, non-radiating, definitely localized to the upper quadrant external to the umbilicus and about 2 inches below the costal margin;

Localized tenderness over the aforementioned area;

Absence of abdominal rigidity;

Vomiting, copious and at times projectile suggesting intestinal obstruction;

Absence of fever and of an accelerated pulse rate;

Absence of shock;

Laparotomy fails to reveal the cause until the adrenals are explored.

With extension of hemorrhage into the perirenal tissues, the classical signs of spontaneous perirenal hemorrhage make their appearance. They are:

1. Sudden sharp pain in the kidney region and upper abdomen, followed by nausea, vomiting, abdominal distention, and other signs of peritoneal irritation simulating intestinal obstruction, usually without fever.

2. Pallor, prostration, and other signs of internal hemorrhage together with the appearance of a perceptibly enlarging tumor mass in the loin makes the diagnosis certain.

The rarity of this condition however causes the most typical cases to go unrecognized. In the few instances where spontaneous perirenal hemorrhage was correctly diagnosed preoperatively, it was made by individuals who had previously seen a similar case.

In the series reviewed by Keele (4), four of the ten cases died in less than twenty-four hours. In the others, symptoms lasted from thirty-six hours to several months. Arnaud (1) quotes a case in which a cyst weighing four pounds was found at post mortem.

The prognosis is dependent entirely on the treatment. Based on the findings by Meyer and Singer (6) and Polkay and Vynolek (7) conservative treatment, when the presenting signs are those of spontaneous perirenal hemorrhage, almost invariably results in a fatal outcome. Surgery offers the only hope.

#### BIBLIOGRAPHY

- (1) ARNAUD, F.: Les hémorragies des capsules surrénales. *Arch. gén. de Méd.*, 4: 5, 1900.
- (2) HALL, E. M., AND HEMKEN, L.: Adrenal glands; clinical and pathologic study. *Arch. Int. Med.*, 58: 448, 1936.
- (3) HYMAN, A.: Personal communication.
- (4) KEELE, D. V., AND KEELE, K. D.: Syndrome of hemorrhagic suprarenal infarction. *Brit. M. J.*, 2: 687, 1942.
- (5) LAVENSON, R. S.: Acute insufficiency of the suprarenals. *Arch. Int. Med.*, 2: 62, 1908.
- (6) MEYER, K. A., AND SINGER, H. A.: Spontaneous perirenal hematoma and aneurysm of the renal artery. *Surg., Gynec. & Obst.*, 45: 300, 1927.
- (7) POLKEY, H. J., AND VYNALEK, W. J.: Spontaneous non-traumatic perirenal and renal hematomas. *Arch. Surg.*, 26: 196, 1933.



# THE ANATOMY AND SURGERY OF THE EDWIN SMITH SURGICAL PAPYRUS

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About fourteen years ago, the late Professor Breasted, head of the Oriental Institute of the University of Chicago, published a translation of a surgical papyrus, the original text of which was believed to antedate the Ebers papyrus and very probably to have been written somewhere between 4,000 and 5,000 years ago. Following Breasted's publication, a number of papers concerning the Papyrus appeared. Most of them were written by orientalists and mainly dealt with the meaning of Egyptian medical terms found in the document. Although much of what will be described in the present article is not new, it may be worth while to give a short account of the injuries and diseases mentioned in the papyrus—especially from the medical and surgical viewpoint.

The Edwin Smith papyrus consists of a text and of commentaries added by some ancient writer a few centuries after the original had been written. Many of the terms employed in the document were no longer clear to the Egyptian reader of a remote day so that—several centuries after the first text had been written—explanatory notes were added and incorporated in the body of the document by an ancient commentator. The entire document must already have been old in the 17th century B.C. when the copy that has come down to us was made.

The papyrus contains the earliest known records of human anatomy and physiology and of the symptoms and treatment of injuries to the head, neck, spine and chest. Unfortunately, the scribe, who some time during the 17th century B.C. made the copy which has come down to us from the old manuscript of the original author's text and ancient commentaries, did not complete his work. He stopped in the middle of a case and thus lost to us a part of the ancient treatise which probably contained a description of injuries to the abdomen and to the lower limbs.

The subject matter is arranged in an orderly manner, beginning with the head and passing successively to the nose, maxilla, temporal region and ear, lips, chin, cervical vertebrae, clavicles, humerus, breast, sternocostal articulations, ribs and thoracic vertebrae.

## ANATOMICAL TERMS FOUND IN THE PAPYRUS

The anatomical terms used in the papyrus are often drawn from commonly observed objects, and are used to render anatomical descriptions more clear. Many modern anatomical terms have a similar origin—e.g., *pons* Varolii, *head* of the femur, *vermiform* appendix, etc.

1. The word "brain" is designated as the "marrow of the skull", and the cerebral convolutions are likened to the rippled surface of metallic slag on the



top of molten copper while it is cooling. The word "brain" is found seven times in the Smith papyrus and is of great interest because it is the earliest reference to that organ anywhere in human records (Breasted). The fact that a word for brain was not known at the time when the original text of the papyrus was written is an item of evidence to support the belief of the extreme antiquity of the document from which our copy was made in the 17th century B.C. The process of embalming of the dead goes back to the Old Kingdom mummies, but at that remote period the brain was not disturbed by the embalmers (Elliot Smith), and it is possible that at that time the organ was not known. Somewhere between the 13th and the 18th Egyptian dynasties (1780 to 1350 B.C.), the embalmers began to remove the brain through the nose by means of some kind of instrument after perforation of the cribriform plate of the ethmoid bone. At that period, therefore, there must have been some word for "brain."

At the early period at which the original document was written, the spinal cord appears not to have been known. In the Egyptian grammar of Gardiner, published in 1927 (i.e., before the appearance of Breasted's translation of the Smith papyrus) there is no term for "spinal cord" or for "nerve." The peripheral nerves must have been seen by the ancient physicians but before the 3rd century B.C. a distinction was not made between nerves, tendons and bloodvessels. Two of the Alexandrine anatomists, Herophilus and Erisistratus, are usually given the credit of having first distinguished between nerves and bloodvessels and of having demonstrated that there is a connection between the brain, the spinal cord and the peripheral nerves.

In one of the cases described in the Papyrus (Case 6) there is to be found the first mention of the meninges ("the membrane enveloping the brain"), and of the cerebrospinal fluid.

These three words—brain, meninges and cerebrospinal fluid—are the only terms referring to the nervous system or its coverings to be found in the papyrus.

2. There are many references to the *osseous system* and to the following bones:

- Skull
  - Temporal
  - Frontal
  - Nasal
  - Maxilla
  - Mandible
- Vertebrae
- Clavicle
- Scapula
- Sternum
- Ribs
- Humerus

Of the 48 cases described in the papyrus, 19 deal with injuries to the bones of the skull. In nine of these, the skull is spoken of without reference to any particular part of the cranial bones, but in one instance the frontal bone and in five cases the temporal bone are specifically mentioned. The word used for temple is to be found 22 times in the papyrus but in most of the cases it is not

used to describe the temporal bone as such but the temporal region. The word used for "temple" or "temporal region" is not to be found in any hitherto discovered document; it appears to be entirely new and an ancient commentator deemed it necessary to add a note on its meaning.

The earliest mention of the cranial sutures, in the history of anatomy, is found in the Smith papyrus, and here again the ancient commentator considered it necessary to add an explanatory note regarding the term used.

In two cases (Cases 6 and 8) there is a reference to the fontanelles—"the weak place in an infant's crown before it becomes whole." It is not surprising that these structures were known, for Egyptian mothers and others must have been acquainted with the fontanelles of new born babies.

The following statements regarding some of the bones deserve mention: The term used for the clavicle or collar bone is a new word not found in any other papyrus (Breasted). In our document it is called "sickle bone." According to the papyrus, the heads of the sickle bones are attached to "the upper bone of the breast,"—i.e., to the manubrium of the sternum.

In several cases of injury to the inferior maxilla, the two rami and the temporo-maxillary articulations are referred to, the connection of the inferior maxilla with the temporal bone being likened to the grasp of the claw of a two-toed bird—the condyloid and coronoid processes being compared to a bird's claws.

In regard to the spine, the text makes it clear that the ancient author appreciated that the spinal column is made up of a number of vertebrae joined together by ligaments. A distinction is made between the cervical vertebrae "the vertebrae of the neck" and the thoracic vertebrae, the "backbone."

In addition to the temporomaxillary and sternoclavicular articulations, the joints between the vertebrae and those between the ribs and the sternum are referred to in the papyrus.

3. The papyrus does not contain any clear reference to the muscles. This is rather surprising because in many instances of injuries to the limbs by battle axe, muscles must have been exposed. In a case of wound of the skull (Case 7) with meningeal symptoms, the text contains an interesting passage: "a gaping wound in the head, penetrating to the bone, . . . the cord of his mandible is contracted." The ancient author gives a commentary on the meaning of the words "cord of his mandible" and explains that they refer to the ligaments at the end of the ramus which are fastened to the temporal bone. Breasted believed that the temporal muscles are here referred to, and if this is the correct interpretation it is the only mention of a muscle in the Smith Papyrus. However, to the writer it seems equally possible that the reference is not to a muscle but to a ligament or to ligaments.

4. As, in those remote times, a distinction was not made between tendons, ligaments and bloodvessels, the papyrus does not contain references to the *vascular system*. However, in the ancient commentary to case 1 there is a remarkable discussion of the action of the heart and of the methods of feeling (counting?) the pulse. In a commentary there is a statement that there are canals from the heart to the head and the upper and lower limbs.

## SYMPTOMS DESCRIBED IN THE SMITH PAPYRUS

Forty-eight cases are described in the text of the papyrus but the statements regarding symptoms and physical signs are very brief. The complete list of cases is as follows:

*Injuries to the head*

- |          |   |
|----------|---|
| Case no. |   |
| 1        | Wound penetrating to the bone   |
| 2        | Wound penetrating to the bone   |
| 3        | Wound penetrating to the bone and perforating the skull   |
| 4        | Wound penetrating to the bone and splitting the skull   |
| 5        | Wound with compound comminuted and depressed fracture of the skull                                  |
| 6        | Wound with compound fracture of the skull and rupture of the membranes                              |
| 7        | Wound penetrating to the bone and perforating the sutures   |
| 8        | Comminuted fracture displaying no visible external injury <sup>1</sup>                              |
| 9        | Wound in forehead producing a compound comminuted fracture of bone                                  |
| 10       | Wound of the eyebrow penetrating to the bone  |
| 11       | Broken nose   |
| 12       | Fracture of the nasal bones   |
| 13       | Fracture extending from the nose laterally to the maxilla and (probably) into the base <sup>2</sup> |
| 14       | Flesh wound in one side of the nose penetrating into the nostril                                    |
| 15       | Wound of the cheek, perforating the bone  |
| 16       | Fracture of bone in the region of the maxilla and zygoma  |
| 17       | Comminuted fracture in the region of the maxilla, perhaps extending into the base                   |
| 18       | Soft tissue wound in the temporal region  |
| 19       | Perforation or fracture in the temporal region  |
| 20       | Compound fracture in the temporal region  |
| 21       | Fracture in the temporal region, probably not compound  |
| 22       | Compound comminuted fracture of the temporal bone   |
| 23       | Wound of the soft tissues of the ear  |
| 24       | Compound (?) fracture of the mandible   |
| 25       | Dislocation of the mandible   |
| 26       | Wound of the upper lip extending into the mouth   |
| 27       | Wound of the chin   |

*Injuries of the neck*

- |    |  |
|----|--|
| 28 | Perforating wound of the throat penetrating into the oesophagus        |
| 29 | Wound of the neck penetrating into a vertebra                          |
| 30 | Sprain of a cervical vertebra  |
| 31 | Dislocation of a cervical vertebra with loss of sensation in the limbs |
| 32 | Displacement of a cervical vertebra without other symptoms             |
| 33 | Crushed cervical vertebra with impaction; loss of sensation in limbs   |
| 34 | Dislocation of the clavicles   |
| 35 | Fracture of the clavicle   |

*Injuries of the upper limb*

- |    |  |
|----|--|
| 36 | Fracture of the humerus                                  |
| 37 | Fracture of the humerus with a wound of the soft tissues |
| 38 | Simple fracture of the humerus                           |

<sup>1</sup> Erroneously called a compound fracture by Prof. Breasted.

<sup>2</sup> Called, by Breasted, a compound comminuted fracture in the side of the nose, but he states that the description indicates that more than the nostril was involved, and that the uppermost part of the maxilla must have been affected by the injury.

*Injuries of the chest*

| <i>Case no.</i> |  |
|-----------------|--|
| 39              | Tumor or ulcer of the upper chest <sup>3</sup> |
| 40              | Wound of the upper chest                       |
| 41              | Infected wound of the upper chest              |
| 42              | Sprain of sternocostal articulations           |
| 43              | Dislocation in sternocostal articulations      |
| 44              | Fracture of ribs (probably compound)           |
| 45              | Bulging tumors on the chest                    |
| 46              | Abscess pointing on the chest                  |
| 47              | Gaping wound in the shoulder                   |
| 48              | Sprain in a spinal vertebra                    |

In 14 of the 48 cases described in the papyrus, there is no mention of any symptom or sign, and the only reference to the lesion is given in the title of the case. In the remaining 34 cases symptoms and signs of the injuries are referred to in more or less detail.

In fractures of the cranial bones and other injuries of the head, a swelling at the site of the injury is mentioned a few times (in Cases 4, 5, 15, 16, 21) while local swelling is mentioned in a case of fracture of the humerus (Case 38) and in three cases of affections of the upper part of the chest (Cases 39, 45, 46) in one of which it appears probable that the swelling was due to an abscess. Stiffness of the neck (inability to bend the head forward on the chest "to look at the shoulders and the chest") is mentioned in nine of fourteen cases of fracture of the vault of the skull, in one case of wound of the neck (Case 29) and in one of displacement of a cervical vertebra (Case 32) but it is not mentioned in three other instances of injury to a cervical vertebra.

Bleeding from the two nostrils and the two ears is described in four cases of fracture of the skull (Cases 4, 5, 7, 8) and bleeding from the nose alone in two cases of fracture of the skull and two of broken nose (Cases 6, 11, 12, 20). Hemorrhage from nose and ear of one side is mentioned in two cases of probable fracture of the base of the skull and one of fracture in the temporal region which may have extended into the base of the skull (Cases 13, 17, 21).

Disfigurement of the injured part is casually specified in a few cases—in two cases of fracture of the nasal bones in which the nose is described as "bent" or "disfigured."

In the majority of instances, signs and symptoms are mentioned without much description but in a few cases there is more detail. Thus in one case of penetrating wound of the head (Case 7) the author states that the patient may be in a state with clammy sweat and feeble heart action or he may have fever and his face be congested. In a case of comminuted fracture of the skull,<sup>4</sup> a remarkable description—for those ancient times—is given of cerebral hemiplegia (Case 8). "His eye is askew on the side . . . of the injury of the skull, and he walks shuffling with his sole on the same side." It is not clear whether

<sup>3</sup> As explained by Prof. Breasted, the word breast does not mean the mammary gland but it indicates the soft tissues of the upper part of the chest and over the sternum. For this reason, I have called lesions in this location lesions of the upper chest rather than of the breast (as done by Breasted).

<sup>4</sup> As already mentioned, this case was erroneously described by Prof. Breasted as one of compound comminuted fracture of the skull displaying no evidence of external injury.

this is a case of recent or old injury; the description of what appears to be a partly paralyzed and spastic lower limb (and in a commentary also the upper limb) makes one suspect that the injury was not a fresh one. The ancient author's statement that both the affected eyeball and the involved lower extremity are on the same side as that of the injury to the head, led Breasted to the conclusion that the case was one of fracture with contrecoup symptoms. It is doubtful whether the mechanism by which ipsilateral pyramidal symptoms are produced in some skull injuries can be explained by contrecoup fracture; aside from this it is of no little interest that the ancient author should have mentioned the occurrence of paralysis on the same side as that of the skull injury. Of course, this does not justify the conclusion that the ancient author was aware of the fact that after a skull injury, paralysis of the limbs usually occurs on the side opposite to that of the bone injury.

In this case, there is another statement which is of very great interest. The authors cautions the reader that the symptoms (disturbance in the power of the lower limb, etc.) are not due to a seemingly spontaneous form of disease—i.e., some internal cause—but due to what may be termed an external cause—i.e., the injury to the skull. One may draw the conclusion that the ancient author knew that similar disturbances, i.e., weakness of a limb, etc., might be caused by an internal disorder. Therefore, we may suspect that he knew something of the symptoms of what we call cerebral hemorrhage or cerebral thrombosis.

Loss of ability to speak is mentioned in five cases (Cases 13, 17, 20, 22, 33). Without making any reference to the learned discussion by Dr. Breasted of the meaning of the Egyptian word used to describe loss of speech, it appears to the present writer that the loss of ability to speak was due to various causes—in one case on account of pain and a resulting difficulty in opening the mouth, in another, to actual aphasia, and in still another, the individual was speechless because he was unconscious.

There is nothing in the papyrus that would justify the belief that the spinal cord was known as an anatomical structure in those ancient times, but in two cases (Cases 31, 33) there is evidence that the ancient author knew that the symptoms due to fracture of the cervical vertebrae might include loss of sensation (and loss of power) in both upper and lower limbs with loss of control of the vesical sphincter and, sometimes, with abdominal distension and priapism.

#### METHODS OF EXAMINATION

The method by which the physician makes a given observation is often not mentioned, but it is evident from the text that in many cases such an examination is presupposed or implied.

Many of the observations were made by inspection and in a few cases the reader is directly instructed to inspect the wound. In other instances the patient is to be told to follow directions. For example, in order to learn whether the patient has a stiff neck (Cases 3, 4, 5, 8, 19, 29, 32) or in order to learn whether the movement of the neck is painful (Case 30) it is implied or the patient is to be actually instructed to look at his chest and shoulders—i.e., to flex the head on the chest.



In a large number of the cases, the ancient author instructs his reader to palpate the wound. In other cases the palpation of the wound is implied,—as when crepitation is felt in fractures of the cranial bones, the inferior maxilla, the humerus or the ribs. Palpation of the wound is evidently recommended in order to determine whether underlying bone has been injured (Cases 1, 2, 18, 27, etc.) or whether there is a depression of bone (e.g., Case 5). The presence of crepitus when the injured part is examined is mentioned in a case of fracture of the nasal bones, one of the upper maxilla, the lower jaw, the humerus and the ribs.

The conclusions to be arrived at from the implied examination are discussed in many of the cases. Thus, the result of palpation of a scalp wound will disclose whether the bone is uninjured or whether it is fractured, whether or not a fracture is depressed or there is a bony defect so that pulsating brain can be felt. The inability of the patient to close his mouth after an injury to the jaw is evidence that the mandible is dislocated and that the dislocation must be reduced. The examination of a wound in the lip will show whether or not the wound is a deep one and has penetrated into the mouth. If a wound in the neck has penetrated into the gullet the patient will choke when he swallows water which will escape through the wound.

Examination of the cervical spine will demonstrate whether there is a dislocation or displacement, or whether the patient has a crushing fracture so that "one vertebra has fallen into the next one." In a remarkable commentary the ancient author explains the mechanism of a crushing fracture of the vertebrae; he states that "his falling head downward has caused that one vertebra crush into the next—which means that he has fallen head downward upon his head driving one vertebra of his neck into the next."

The ancient surgeon also appears to recognize that in fractures of the clavicle, the bone fragments usually override so that the bone seems shortened. As we shall see, he gives instructions how the overriding fragments can be brought into proper relation to each other.

In one of the cases, the ancient author states the patient's heart may be beating feebly (Case 7) and one wonders by what method of examination that conclusion was arrived at. Were the pulsations of the apex of the heart transmitted to the chest wall felt or was the conclusion reached from feeling the pulse? In Case 1 the ancient commentator explains to some degree what is meant by the word "examination." Apparently, the ancient author knew that by placing his hands or fingers at various points on the body of the patient, he could gain information regarding the "action of the heart," and he appreciated that no matter where located the injury might have an effect upon the heart and that the heart's action was an indication of the patient's general condition.<sup>5</sup>

In a number of the cases (Cases 7, 24, 28, 39, 41, 47) mention is made of the fact that the patient has fever. This was probably determined by palpation

<sup>5</sup> It is beyond the scope of this paper to discuss the question whether the ancient surgeon felt the strength of the pulse or whether he also investigated its rate, and if the latter was the case, the nature of the instrument used for time measurements. These matters are interestingly discussed by Prof. Breasted.



of the surface of the body or of the wound, as indicated in Case 39 where the statement is made that the patient "is hot when thy hand touches him" and in Case 45: he is very cool there being no fever at all . . . "when thy hand touches him."

#### METHODS OF TREATMENT

In 16 of the 47 cases which are described in the Smith Papyrus, no treatment of any kind is suggested,—in most of these sixteen the case is considered hopeless. However, in a few instances the advice is given to pursue a waiting policy and to begin treatment only if the patient shows signs of improvement.

In five cases of fracture of the skull (Cases 4, 7, 8, 17, 20) in one of maxillary fracture (Case 16) and in one of displacement of a cervical vertebra (Case 32) the advice is given to keep the patient in a sitting position until the outcome is clear—"until he has reached a decisive point." The ancient author does not explain why the sitting position is recommended, and one is led to wonder whether—especially in cases of cranial injuries—this position, which would tend to diminish intracranial pressure, had been found clinically to be of advantage.

Whenever treatment is recommended it is either by topical remedies or by surgical procedures or a combination of both of these.

*Treatment by topical applications or remedies.* In a number of instances of wounds, the reader is advised to apply fresh meat at first and later to apply lint soaked in grease or honey held against the affected part by bandages. The substances preferred for wound dressings appear to be fresh meat as a preliminary followed by grease, honey or an unknown substance. The application of fresh meat to wounds gives rise to the speculation whether the meat (muscle) may have been used for its hemostatic effect. This is reminiscent of the comparatively recent lay custom to apply meat to the ordinary "black eye."

These substances were to be bandaged on the affected part and the dressings changed daily. In several cases of fracture of the nasal bones plugs of lint soaked in grease are to be introduced into the nasal passages after blood clots have been removed.

In a case of inflamed wound of the chest wall (Case 41) topical applications to cool and dry up the wound followed by poultices are advised, while in a case of possible abscess of the chest wall (Case 46) cooling applications followed by astringents and by poultices are recommended. Most of the ingredients used for the applications are not identified, although Breasted mentions willow (salicin) acacia, sycamore and some mineral substances. In only one case (Case 9) is there a recipe for external application accompanied by the instruction to repeat a magical charm when the remedy is being applied. Prof. Breasted believes that this is a case from one of the so-called *recipe papyri* which has in some way found its way into this surgical treatise. The lint that was used for the topical applications was made of some vegetable tissue and was held on by means of bandages. The embalmers were skillful in making and applying bandages, and according to Breasted, Elliot Smith and others, it is probable that linen bandages for surgical use were also made by embalmers.

*Surgical Treatment.* In seven cases (Cases 3, 10, 14, 23, 26, 28, and 47) the ancient author advises that the edges of a wound should be drawn together by stitching. Breasted states that, as far as is known to us, this is the first mention in ancient surgery of the use of sutures, and he goes to some length to explain his conclusion that the word used by the ancient author really means "stitching." In some instances, the ancient author speaks of drawing together the edges of a wound by stitching and further he advises that if the stitches have become loosened, that the wound edges should be approximated by strips of adhesive linen. It is probable that sticky resin which, as we know, was much used in the process of embalming, was applied to the linen strips.

*Treatment of Fractures.* The success of Egyptian surgery in immobilizing fractured bones has been demonstrated by the large number of well united fractures found in ancient skeletons. Many illustrations have been published by Elliot Smith which show that splints covered by linen were used for the immobilization of the affected limbs. The Smith papyrus contains only a few statements regarding the reduction of fractures and their immobilization by splints, but—because they show that the ancient surgeons had some idea of the mechanism by which fractures should be reduced and the bone fragments held in place—these statements are of no little interest.

Cases 10 and 11 are instances of fracture of the nasal bones. The nasal passages are first to be cleaned of blood; then a plug of linen saturated with grease is to be introduced into each nasal passage and stiff rolls of linen applied on the outside of the nose. If the nose is bent and disfigured, the deformity should be reduced before the plugs of greased linen are inserted and the stiff rolls of linen applied on the outside. Essentially, this is the modern method of treatment of fracture of the nasal bones with deformity of the nose.

Case 35 is one of fracture of the clavicle. The patient is to be placed flat on his back with something folded between his shoulder blades. Then the shoulders are bent backwards and spread in order that the bone fragments are stretched apart until the deformity is reduced. Then two splints are to be applied to the upper arm,—one on the inner side and the other on the under side. Topical remedies are to be applied and the splints kept in place by bandages.

In fractures of the humerus (Cases 36 and 37) the patient is to be placed "prostrate on his back with something folded between his two shoulder blades." The shoulders are to be spread out so that the upper arm is stretched out and the ends of the bone fragments fall into normal relation to each other. Two splints are then to be applied—one on the inner and the other on the under surface of the arm—and these are to be held in place by bandages.

With only a little left to the imagination, the modern reader may gather that for those remote times, the ancient author had a remarkable understanding of the treatment of fractures.

Likewise, although the evidence is meagre (one case: no. 25), one may conclude that the treatment of some dislocations was also a rational one. The method for the reduction of a dislocation of the lower jaw (Case 25) is that which is still in use: The bone is grasped between the two thumbs introduced

into the mouth and the other fingers on the outside under the chin, and the dislocation is reduced. It is probable that the manipulation by which the articular surfaces were brought back into their normal position was similar to that used today. In a case of dislocation of the clavicles, the ancient author does not state how the dislocation is to be reduced but he makes a distinction between a forward dislocation which is reducible and a backward dislocation with an external wound which is a hopeless condition.

The only other surgical procedure mentioned in the papyrus is in the discussion of a case of post-traumatic (?) boil or abscess or ulcer on the chest wall. Here, the author recommends that the affected part should be treated with the "fire drill." Breasted concluded that the procedure was cauterization of the area. However, it seems to the present writer that the condition may well have been an abscess because in the same paragraph in which the "cauterization" is advised, the ancient author states that one should not prevent the lesion opening of itself for "every sore that opens of itself dries up as soon as it is open."

#### COMMENT

There is a striking difference between the surgery of the Smith papyrus and the medical therapy of the ancient papyri thus far unearthed, translated and interpreted. The Smith papyrus demonstrates that at a period in which internal medicine was still demonic and interwoven with magic and incantations, surgical lesions were already accurately observed and in many cases a rational therapy was advised. In only one case in the entire papyrus—a case of fracture of the skull—the treatment consists of a curious mixture of superstitions: a poultice for drying up the wound is to be made from the egg of an ostrich and a charm is to be said over the wound. The treatment of this case is unlike that described in any other part of the surgical papyrus and reminds one of what is regularly found in the medical papyri of a later age.

The Smith papyrus contains the earliest known references to the brain, to the effects of a cranial injury upon the power of the limbs of one side, and to the effects of injury to the vertebrae upon the sensation and power of the limbs of both sides of the body.

The few instances in which the ancient author indicates how fractures of the long bones are to be reduced and the manner in which the affected parts are to be immobilized, is illuminating of the surgical practices of those remote days. It is surprising that mention is made only of fractures of the humerus in the upper limb and that there is no reference to fractures of the bones of the forearm. Elliot Smith who had seen more than one hundred fractures in ancient Egyptian bodies, states that "fracture of the forearm—as a rule the left ulna, but often both bones, and sometimes in both arms—has always been exceedingly common in Egypt in comparison with the incidence of other fractures. This is true of every period from the earliest known prehistoric times up till the present."

In the treatment of certain fractures of the long bones, the use of two splints is advised in the Smith papyrus but Elliot Smith states that usually four splints were used, and that these splints were either of wood or of bark covered by linen bandages.

The Smith papyrus is written in aphoristic style but it is more than a series of aphorisms because of the descriptions of symptoms and of methods of treatment. It may be called a skeleton textbook which contains much of what was known of injuries in those ancient days. It is not only a practical treatise but also a demonstration of Egyptian idealism. Withington, in his artistic and philosophical "Medical History," makes the statement that the ancient Egyptians were "essentially a matter of fact race; types of those practical people of whom it has been well said that they practice the errors of their fathers." To the Greek, he says, science was a majestic goddess, a clear-eyed Pallas Athéné; to the Egyptian she was a domestic cow, good only for what could be got out of her. Breasted acknowledges that before his translation of the Edwin Smith Papyrus, most Egyptologists—himself included—had believed that Egyptian medicine and surgery was purely utilitarian and materialistic. The ancient author of the Smith papyrus certainly was an exception. The author and the ancient commentator both describe and explain facts concerning hopeless injuries apparently for their scientific interest alone. The conclusion arrived at by Professor Breasted is therefore justified—that even at this early period—almost five thousand years ago—knowledge was cultivated for its own sake. The Edwin Smith Surgical Papyrus is therefore the oldest milestone yet discovered on the long road to modern medicine and surgery; it is a document of great human interest as well as an important contribution to the history of medicine and surgery.

#### REFERENCES

1. BREASTED, JAMES H.: The Edwin Smith Surgical Papyrus. Chicago, University of Chicago Press, 1930.
2. BRYAN, CYRIL P.: The Papyrus Ebers. New York, D. Appleton & Co., 1931.
3. ELLIOT, SMITH G.: The Most Ancient Splints. Brit. M. J., 1908.
4. ELLIOT, SMITH G., AND DAWSON, WARREN R.: Egyptian Mummies. London, G. Allen & Unwin, 1924.
5. WITHINGTON, EDWARD T.: Medical History. London, Scientific Press, 1924.

## METABOLIC ASPECTS OF THE SHOCK PROBLEM

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Regardless of its cause, shock is an ever present problem for the surgeon and clinician. War greatly accentuates interest in this problem, for every battle casualty is a potential candidate for wound or hemorrhage shock which almost invariably would lead to a fatal outcome unless adequate and early therapy be available. Although great progress has been made in our understanding of the mechanisms and treatment of shock, progress which is reflected in the improvement in mortality figures among the wounded in World War II, much is still to be learned before shock can be eliminated as a serious cause for concern in the operating room or on the battlefield. It is now well recognized that, regardless of the initiating factors involved, almost all cases of shock are characterized by a decreased circulating blood volume. The early correction of this defect by transfusion with whole blood, plasma, or other suitable blood substitutes is the keystone of modern shock therapy. But it is realized equally well that, if transfusion is delayed or is inadequate in the beginning, a state may develop in which no amount of restoration of fluid will save the victim. This condition has become known as the "irreversible" stage of shock and as such represents a major therapeutic problem. Profound anoxia and a markedly hypodynamic circulation which cannot be corrected by restoring the blood volume are important features of "irreversible" shock. If not readily corrected by the simpler cardio-vascular and respiratory reflexes, anoxia soon begins to impose a severe strain on the metabolic activities of the tissues. Whether the metabolic alterations due to anoxia are to be considered as initiating or as perpetuating factors for "irreversible" shock is not yet known. Nevertheless, it would seem that a careful analysis of the biochemical features of shock is now necessary if we are to develop a rational basis for the therapy of "irreversible" shock. It is the purpose of this report critically to review some of the recent studies bearing on this subject.

Many significant, although often isolated, observations have been made in the past on the biochemical changes in shock, but until quite recently the major emphasis in shock research has been on hemodynamics. And rightly so, for there is little doubt that the circulatory changes are of primary significance in the establishment of the shock syndrome. Chemical changes had been investigated primarily to reveal the possible existence of a toxic factor as the cause of traumatic and burn shock. Other changes had been clearly recognized as the end results of tissue anoxia and as such have been dismissed as "terminal" if they could not be reversed by whatever methods of therapy were in vogue at the time.

From a biochemical standpoint there does not appear to be a great deal of



difference between the various types of shock, for the common denominator in all is tissue anoxia. Yet, more or less subtle differences are bound to occur, depending on such factors as the amount of tissue damaged in traumatic and burn shock as compared to hemorrhage shock, the site of the tissue damage (i.e., visceral or peripheral), the presence of elevated body temperature, as in the shock accompanying acute infections, etc. Hemorrhagic shock is the most simple biochemically, for all the changes observed can be attributed exclusively to circulatory insufficiency and adjustments thereto.

In any consideration of the chemical changes during shock it is of utmost importance to establish the time relationships between these changes and the well known hemodynamic alterations. Among many workers in the past there has been an unfortunate tendency to isolate from the blood single constituents, potassium for example, and to attribute to them an etiological rôle in the development of the shock syndrome. In so doing, they usually ignored the more fundamental tissue changes which had produced the blood changes and which had occurred because shock (anoxia) was already established.

The chemical changes of shock can be divided into three overlapping categories. Firstly, there are those which presumably precede the circulatory alterations, are considered to have their origin in damaged tissue, and have often been incriminated as "toxic factors." The voluminous and controversial literature on the chemical isolation of so-called toxic factors will not be considered in this review. Secondly there are more subtle biochemical changes in the nature of homeostatic reactions to stress. With few exceptions, these are so rapidly overshadowed by the more dramatic effects of tissue anoxia that they are difficult to isolate and evaluate. The third group, representing those changes due to tissue anoxia, has been the subject of the most intensive study in recent years. The anoxic changes are complicated by the fact that not all tissues of the body are subjected to the same degree of oxygen deprivation at the same time or rate during shock—and that different tissues show different degrees of sensitivity to anoxia. Circulatory adjustments occur during shock so that the brain, which is the tissue in the body most sensitive to anoxia, maintains its circulation as long as possible, while the extremities early become anoxic owing to peripheral vasoconstriction. In addition, certain other organs may become anoxic earlier than others because of the intrinsic nature of their blood supply. The liver, whose blood supply is predominantly venous, is an example. Moreover, such factors as the previous nutrition of the organism may make a difference in the response of its tissues to anoxia. Thus, for the proper understanding of the chemical nature of shock these changes must be studied not only in terms of the functioning of the whole animal, but also of its individual parts. And finally, it must always be borne in mind that the demonstration of the failure of one or more, or even all functions of any given organ during shock does not necessarily prove that this loss is critical, though it may be if it persists long enough. Since the chemical changes due to tissue anoxia are the most important in irreversible shock, they will be considered first and in greatest detail.



## METABOLIC CHANGES DURING SHOCK

*a. Blood.*—The problem of metabolism in shock hinges on the reactions of the organism to anoxia. In the beginning these changes are mostly reflex in nature, mediated through the autonomic nervous system, and involving the circulatory system (38). They are designed to make best use of a decreasingly available blood supply and to conserve as long as possible an adequate circulation to vital organs such as the brain and heart. Splanchnic and peripheral vasoconstriction occur through reflexes mediated by the sino-aortic area, vasomotor center, and sympathetic outflow, counteracting the tendency for the blood pressure and cardiac output to fall, and maintaining cerebral and cardiac circulation. But these reactions occur at the expense of further oxygen deprivation of the tissues in which vasoconstriction occurs. As anoxia progresses, alterations on a broader level are necessary to maintain tissue integrity. The body temperature begins to fall and the overall metabolic rate decreases (4, 14, 44, 53, 73). There is a shift from aerobic to anaerobic metabolism at the cost of a loss of efficiency in terms of energy yield per unit of substrate used. If this last reserve fails, the integrity of the cellular enzymes involved in energy yielding reactions is probably disturbed, and serious, if not irreversible, damage to the tissue ensues. All these changes are bound to be reflected in the composition of the blood during shock.

The last column of Table I summarizes some of the blood chemical changes during shock. Probably the earliest is a rise in blood sugar due to epinephrine-induced glycolysis in the liver, a reaction which may be considered homeostatic. This rise parallels the other evidences of sympathetic discharge, but, as will be described below, is not an inevitable concomitant of shock. Most of the other changes appear to follow the decrease in venous oxygen content, but this relationship is often obscured because the oxygen content of venous blood from different parts of the body is not the same at any given moment during shock (32, 92). In general, however, the venous oxygen falls progressively during shock, while the arterial oxygen remains normal until the very end when it may fall coincident with respiratory failure (5, 14, 32, 35, 50, 73, 92). Venous blood from an extremity is usually the first to show a decline in oxygen content, followed by that of the portal, hepatic and renal veins, while the venous oxygen content from the brain is probably the last to decrease (32, 92). The venous carbon dioxide content usually falls slowly at first, but late in shock may drop sharply, reaching very low values (3, 15, 35, 50, 53, 73, 92). The arterial carbon dioxide content also decreases, but at a slower rate than the venous one. The decline in carbon dioxide is largely due to an increase in the fixed acids of the blood such as lactic acid (3, 31, 50, 62, 69, 75, 76), pyruvic and other alpha-keto acids (3, 31, 41, 69) and amino acids (31, 39, 54, 60, 83). Relatively late in the course of the above changes a shift in the blood pH to the acid side may occur (1, 3, 35, 75). Changes in nitrogen metabolism are indicated by rises in the blood concentrations of polypeptides (26, 37, 82), amino nitrogen, urea, creatine (6, 39, 82) uric acid (69, 82) ammonia (77) and non-protein nitrogen in general (8, 15, 69, 90), as well as by the increased urinary excretion of nitrogen

and sulphur after shock due to trauma, burns and hemorrhage (15, 19, 21, 29, 52, 83). Finally, there occur significant elevations in the blood potassium (16, 50, 63, 94) and phosphate (3, 13, 24, 44, 55, 69). These blood and urinary changes in shock represent the summation of reactions due to anoxia of tissues in general and the effects of decreased circulation and anoxia of such organs as kidney and liver with consequent alterations in their function. In order to understand the overall metabolic picture, it is necessary to view it in terms of the contributions of different tissues and organs.

*b. Peripheral tissues muscle.*—During the development of shock of any type it is generally the extremities which are affected first because of the early occurrence of reflex vasoconstriction. Following hemorrhage, any changes in the peripheral tissues may be safely attributed to the effects of impaired circulation alone, but after trauma and burns there may be superimposed other changes which are characteristic of the injury. In terms of bulk and metabolic activity, muscle makes up the greater part of the peripheral tissue and, as such, probably is the site of most of the chemical changes occurring in the extremities during shock. Nothing is known at present of changes occurring in such other tissues as skin, fat, connective tissue and bone.

Compared to other body tissues, muscle is quite resistant to anoxia and may remain viable after relatively long periods of circulatory restriction. Bollman and Flock (13) have shown that rat muscle will recover even after three hours of complete obstruction of the circulation. Even under normal circumstances, i.e., exercise, muscle is called upon to function under anerobic conditions for varying periods of time until circulatory adjustments can occur. During the anaerobic phase of muscle metabolism, energy is derived largely from glycolysis, the end product of which is lactic acid. Compared to aerobic respiration, glycolysis is much less efficient, since four to seven times as much substrate must be utilized anaerobically to yield only about one half as much energy as is produced under aerobic conditions (59). Thus, during anoxia one may expect a high rate of consumption of glucose and an accumulation of lactate and pyruvate in muscle. Furthermore, anaerobiosis will be associated with a tendency for inorganic phosphate to be released from its organic combinations. And, finally, Baetjer has shown that under conditions of local *anoxia in muscle* potassium escapes from the cells. In the case of shock, all the changes in the blood which would be anticipated in view of the above reactions have been demonstrated to occur, but special methods have had to be designed to demonstrate some and to prove their origin in muscle. The elevations in blood lactate, pyruvate, phosphate, potassium and creatine have already been mentioned.

Under ordinary circumstances with an adequate supply of glycogen in the liver and the adrenal medullae are intact, shock will produce an early rise in the blood sugar due to hepatic glycogenolysis by epinephrin. This is usually maintained until late in shock and compensates for the increased glucose requirement of anoxic muscle. Terminally, however, when the glycogen supplies have become depleted, the blood sugar generally falls (17, 31, 42, 51, 85). If the liver glycogen of rats is depleted beforehand by fasting, shock results in

little or no rise in the blood sugar at first, and a relatively early fall as shock progresses (31). If the adrenal medullae are removed and epinephrin secretion prevented, hemorrhage produces a prompt fall in the blood sugar (31). Finally, by making use of the eviscerated rat, we have demonstrated conclusively that an increased glucose utilization by peripheral tissues (muscle) occurs during shock (78). In this preparation the gastrointestinal tract, spleen and pancreas were removed and the liver was excluded from the circulation, thereby eliminating the major source of glucose for the organism. Any changes in blood constituents would therefore represent processes going on in the remaining tissues, chiefly muscle. Since the liver had been eliminated and no other adequate source of carbohydrate was available, the blood sugar declined progressively as it was utilized and the animal eventually became hypoglycemic and died. As the blood sugar fell, the blood lactate and pyruvate rose only slightly and the ratio of lactate to pyruvate remained constant until terminally when there was a sharp rise due to the onset of convulsions. The maintenance of a normal ratio of lactate to pyruvate, as the blood sugar fell, suggested that glucose was being metabolised normally by muscle in the eviscerated preparation. In contrast to this behavior of the control eviscerated rat, hemorrhage in the eviscerated rat produced a prompt and very much more rapid fall in the blood sugar and a pronounced rise in both lactate and pyruvate. The blood lactate rose more rapidly than the pyruvate so that the lactate/pyruvate ratio increased. The sharp fall in blood sugar in the eviscerated rat in shock indicates the rapid utilization of carbohydrate in the periphery during shock while the mounting lactate/pyruvate ratio demonstrates that the metabolism of carbohydrate is largely anaerobic (36).

Since the phosphorus-containing compounds represent the main energy reservoir for carbohydrate metabolism in muscle as well as elsewhere, their fate during shock is of considerable interest. Of these compounds adenosine triphosphate (ATP) is among the most important as a source of energy-rich phosphate bonds (58) while the breakdown of creatine phosphate in muscle supplies much of the phosphate to maintain the ATP reservoir. Under normal circumstances the balance between the various phosphate compounds is very discretely maintained so that there is always an adequate supply of ATP and other energy-rich phosphate bonds to keep the metabolic wheel turning. In the case of shock there are few data in the literature to indicate whether the supply or rate of turnover of ATP and other energy-rich phosphate compounds may be inadequate. However, there is evidence of some alteration in phosphate metabolism. Serum inorganic phosphate rises very soon after muscle trauma and burns (13, 24, 69), and somewhat later after hemorrhage (56). Aub and Wu (6) and Neufeld and his co-workers (69) noted a sharp rise in blood creatine after trauma and Glenn and his collaborators (39) reported it after burns in both blood and lymph, indicating breakdown of one of the important phosphorus containing compounds. Bollman and Flock (13) have confirmed this in studies on muscle phosphate in rats. In animals suffering from tourniquet shock they found a definite increase in the inorganic phosphate and a moderate decrease in creatine

phosphate contents of the muscle of the untraumatized limbs. No significant changes in ATP were found in these same muscles.

Various investigators, including Fleisch (33), Drury (23), and Zipf (93) have commented on the vasodilating properties of ATP and its breakdown products. Recently, Green and Bielchowsky (45) have described ATP and pyrophosphate extracted from normal muscle as shock-producing factors, when injected intravenously, and suggested that they may be released from muscle following trauma. However, ATP has not been found in plasma of animals in shock and the evidence is against it being released as such. Bollman and Flock found ATP and creatine phosphate to be completely broken down in the leg muscles within three hours after application of tourniquets to these legs in rats. Escape of ATP into the blood, therefore, cannot be responsible for the shock which follows release of the tourniquets.

Striking changes also occur in the nitrogen metabolism of the peripheral tissues during shock, indicating a rapid breakdown of protein. After burns (26) and muscle trauma (37) polypeptides have been reported in the blood, but these data have never been adequately confirmed. Of greater significance are the elevations in the blood amino nitrogen, which consists primarily of amino acids plus some uric acid, glutamine and other undetermined amino nitrogen compounds. As will be mentioned later this amino nitrogen accumulation in the blood is due partly to failure of hepatic function. However, we have also shown that the rise in blood amino nitrogen is greater than would be expected from complete hepatic failure alone, indicating that there must also be an increased production of amino nitrogen compounds in the periphery (31). This impression was confirmed by comparing the rate of amino nitrogen rise in the blood of eviscerated (hepatectomized) rats with that in eviscerated shocked rats (78). In the eviscerated rat there is a steady increase in amino nitrogen due to the absence of deamination by the liver. When shock is induced by bleeding in the eviscerated rats, the amino nitrogen rises much more sharply, indicating that amino acids are being produced at a greater rate by the peripheral tissue through protein catabolism. The enhanced protein breakdown results not only from the generalized tissue anoxia of shock itself, but also from local trauma or anoxia which may in turn lead to shock. Glenn, Muus and Drinker (39) have reported an early rise in amino acid nitrogen in the lymph draining from burned tissue in calves. Hoar and Haist (54) noted that after the release of pressure cuffs on the legs of dogs the plasma amino nitrogen began to rise before the blood pressure had fallen to shock levels. They attributed the primary rise in amino nitrogen values to processes going on in the injured tissues.

The significance of these many changes in the peripheral tissues is by no means clear. A decrease in muscle tone which may result would be serious only if it decreased the venous return from the extremities. On the other hand, these metabolic changes may have important effects in another sense. The greatly increased carbohydrate utilization decreases the amount of glucose available for the brain. The acidosis, which probably arises almost completely



from the muscle changes may be a continuing factor in the shock, hence it may be of importance to correct it.

c. *The Liver*.—In diversity and scope of function the liver occupies a position of central importance in metabolism. Among organs, it is unique in receiving its major supply of oxygen by vein. Under normal circumstances 70 to 80 per cent of the blood supplying the liver is carried by the portal vein (49, 65) and McMichael estimates that this accounts for about 60–65 per cent of the oxygen supply of the liver. Both the hepatic artery and portal vein are under neural control so that impairment of flow in one may lead to a compensatory increase in the other. Further, there is evidence that blood may pass through the spleen to the portal vein relatively unchanged in its oxygen content and thereby help maintain the portal vein oxygen in case of emergency. Splenic vein flow accounts for 10–35 per cent of the total portal flow (64). Despite these potential safety measures there is good reason to suspect that the liver might begin to suffer quite early from oxygen lack in shock and that some of its manifold metabolic functions might be impaired thereby. Decreased blood flow in the intestines has long been recognized as a feature of shock (74). Blalock and Levy (10) noted a 53 per cent decrease in portal vein flow after only a moderate hemorrhage and Wood, Mason and Blalock (92) reported an early drop in the portal venous oxygen content after hemorrhage.

Recently the problem of the rôle of the liver during shock has been the subject of a series of reports from this laboratory (31, 32, 79, 80). Use was made of the fact that the amino acid content of the blood is largely dependent on the integrity of the liver, which is the chief site of amino acid deamination. When liver function is normal, relatively large amounts of amino acids may be introduced parenterally without causing more than a transitory rise in the blood amino nitrogen (86). If the liver is removed or its function impaired, amino acids will accumulate in the blood (12, 66). Renal function does not appreciably influence the amino acid levels for even after nephrectomy they show very little increase in the blood (11). It is obvious, therefore, that in any pathological condition the blood amino acid content will be determined primarily by the capacity of the liver to deaminate amino acids or to synthesize protein and secondarily by the rate of amino acid production through protein catabolism. In the case of shock it has already been mentioned that the amino acid content of the blood rises and that there is a rapid protein breakdown in the periphery. When the first observation was made, it was presumed that there was a failure in hepatic function due to circulatory insufficiency and anoxia (31). To prove this, it was necessary to show (a) that the liver is subjected to anoxia during shock, (b) that the amino acid changes can be correlated with the anoxic phase of shock and (c) that anoxia can impair the liver's ability to metabolize amino acids. Using rats and cats, we found that the oxygen saturation of the portal venous blood fell during hemorrhage. In cats, where it was possible to measure it, the hepatic vein oxygen saturation showed an even earlier drop demonstrating that the liver becomes very anoxic during shock and that the hepatic artery cannot compensate for the decrease in oxygen carried by the portal vein. A

highly significant correlation was found between the portal venous oxygen saturation and the blood amino nitrogen. This correlation was more significant than that between the amino nitrogen and the peripheral venous oxygen saturation or the blood pressure, suggesting a close relationship between the supply of oxygen to the liver during shock and its ability to handle amino acids. Further, it was shown that the *in vitro* oxygen consumption of liver slices from animals in shock was reduced and that the degree of reduction was proportional to the height of the amino nitrogen in the blood. To determine whether anoxia itself would influence hepatic function, the effects on the blood amino acids of partial and complete occlusion of the circulation to the liver were studied. Ligation of the hepatic artery of the rat was found to have no effect on the blood amino acids. Nor did hemorrhage in the hepatic artery-ligated rat cause any greater rise in amino nitrogen than it did in the intact animal. This suggests that the arterial blood supply to the liver in the rat does not play a crucial rôle in the response of that organ to shock. If the gastrointestinal tract and the portal vein were removed, leaving the hepatic artery as the sole blood supply of the liver, this organ still maintained its ability to handle amino acids, although its margin of safety was very low. By applying a clamp to the hepatic artery of this preparation the effects of total occlusion of the blood supply to the liver for varying periods could be studied. It was found that under these circumstances the blood amino acids rose during the time that circulation was cut off, but returned to normal when the clamp was removed, provided it had been in place less than forty-five minutes. If the liver was kept anoxic more than forty-five minutes, its ability to metabolize amino acids was irreversibly damaged. This was confirmed by showing that the *in vitro* oxygen consumption of liver slices from clamped livers was reduced at the end of the anoxic period, but returned towards normal during the next two hours, provided the clamp was removed before forty-five minutes, but not if the liver were kept anoxic longer (80). These data show that if the liver is kept anoxic long enough, its ability to metabolize amino acids is seriously damaged. Grieg (47) has confirmed this in studies on the *in vitro* metabolism of amino acids by anoxic liver slices. We may thus conclude that during shock the liver may be subjected to considerable anoxia and that during this period of restricted circulation its function is deranged, at least in respect to the metabolism of amino acids, this damage becoming serious if anoxia persists too long. Protein breakdown in the liver because of anoxia must also be considered as a possible part of this picture, although direct data on this point are not available. Hoar and Haist (54) have recently confirmed the presence of a disability in amino acid metabolism by the liver in rats and dogs during traumatic shock.

Although there have been few systematic studies of liver function in shock and relatively little attention has been paid to the liver *per se*, there is ample evidence in the literature indicating wide spread disturbance in liver function during shock. Other substances which are metabolized or produced primarily in the liver have been found to be altered in the blood in such a manner as to suggest hepatic involvement. Thus, uric acid (69, 82) and ammonia (77),



both of which are metabolized chiefly by the liver accumulate in the blood much as do amino acids. Mylon, de Suto Nagy and Winternitz (67) have found prothrombin and fibrinogen formation depressed during shock. Ebert and his associates (27) have reported plasma protein regeneration to be diminished after severe hemorrhage. Nishimura (70), using the azorubin-S excretion test, found impaired liver function during shock produced by intestinal perforation.

Glycogen formation and breakdown, very important liver functions, have been studied in some detail by Haist and Hamilton (51). The earlier finding of Aggazzotti (1) that the liver glycogen is reduced after hemorrhage, was confirmed by these workers in shock due to limb clamping and by Neufeld, Toby and Noble (69) in the shock caused by tumbling rats in the Noble-Collip wheel. Haist and Hamilton (51) further showed that, following the administration of sugar by stomach tube, the shocked rats were unable to store glycogen in a normal manner, despite a high blood sugar and normal absorption of glucose from the gastrointestinal tract. The ability to store glycogen in the liver was not influenced by the administration of insulin, yet the blood sugar fell. Although the liver glycogen is reduced during and immediately after shock, we have found no significant differences between the liver glycogen of rats twenty-four hours after a moderate hemorrhage and control rats fasted the same length of time as the bled ones (31). It is thus apparent that if the animal survives it is able to restore its liver glycogen within twenty-four hours.

Examination of autopsy material in both animals and humans also gives evidence of liver damage. Central liver necrosis was noted by Weston and his co-workers (89) after severe hemorrhage in dogs. Other observers have also described hepatic cell degeneration (25, 28, 68). Elman and Lischer (28) noted a decrease in stainable cytoplasm in the liver cells of human and dogs which they attributed to loss of protein. Clear-cut evidence of hepatic dysfunction of hepatic dysfunction in clinical shock is occasionally seen in the not too well-defined hepatorenal syndrome. No adequate studies of liver function in clinical shock exist.

Despite these widespread changes in liver function it must be emphasized that it has not yet been proven that the loss of any or all of these functions is a critical factor in survival. In all likelihood, the length of time during which the liver is anoxic is the determining factor, for moderate periods of loss of function are quite compatible with recovery.

*d. The Kidney.*—Failure in renal function, manifested by oliguria or even anuria, has long been recognized as a feature of shock in man and animals and has been attributed to decreased blood flow through the kidney. Lauson, Bradley, and Courmand (56) have recently studied the renal circulation in shock in humans and have demonstrated a reduction in the rate of glomerular filtration and effective plasma flow. Since the decrease is greater than can be accounted for solely on the basis of reduced arterial pressure, they suggest that active constriction of the renal vessels takes place. Renal circulation generally improves with therapy, but lags behind the increase in cardiac output and blood pressure. Usually the renal shut-down is temporary, but it has been

noted clinically by the above authors and confirmed experimentally in dogs by Phillips and Van Slyke (72) that, if renal anoxia persists long enough, irreversible renal damage occurs. The observance by Penner and Bernheim (71) of ischemic cortical necrosis in the kidneys of patients dying after prolonged vascular failure further emphasizes the potential dangers of prolonged renal anoxia. Renal failure in the crush syndrome is on a somewhat different basis and will not be considered here.

Renal failure will, of course, be reflected in the blood. Urea and other non-protein nitrogen compounds which depend on the kidney for their elimination will accumulate. Potassium and inorganic phosphate released from anoxic tissues will not be excreted normally. The acidosis will not be counteracted by the kidney which would normally rapidly excrete the organic acids in the blood and form ammonia to conserve base.

Table I summarizes the pertinent data on the metabolic interrelationships between the peripheral tissues, liver, and kidney during shock and their reflections in the blood chemistry. It may be noted here that changes in fat metabolism during shock have not been mentioned. This is due to the paucity of data on this subject and not to its lack of importance. Particularly in the liver, a considerable proportion of the oxygen uptake by tissues is associated with the metabolism of fat and several of the enzyme systems involved in these processes have been found to be quite sensitive to oxygen lack. It is quite possible that investigation may reveal changes in fat metabolism during shock which are of considerable interest and importance.

#### TISSUE METABOLISM AND ENZYME SYSTEMS IN SHOCK

In the previous paragraphs evidence has been presented indicating widespread disturbances in intermediary metabolism during shock. In the last analysis all processes of metabolism depend on the integrity of enzymes and enzyme systems for their normal function. Hence, the investigation of the metabolism of isolated tissues and of the status of the various enzyme systems in these tissues during shock is of importance and may yield a clue as to the fundamental nature of the metabolic derangement during this condition.

Studies of this type have been performed only quite recently, and only a few reports of this work have appeared. Some of these reports are contradictory owing largely to technical differences in carrying out the experiments. In general, two types of investigation have been conducted. In one the oxygen consumption ( $Q_{O_2}$ ) and sometimes the rate of glycolysis of isolated tissues from animals in shock or of tissues subjected to anoxia *in vitro* have been measured and the effects on the  $Q_{O_2}$  of the addition of various substrates and enzymes compared. In the other the concentration and the state of integrity of various enzymes and coenzymes in the tissues of animals in shock have been studied. It should be recognized at the outset that measurements of this type may be of limited value unless all factors are taken into account. The  $Q_{O_2}$  of tissue represents the overall oxygen consumption due to a variety of metabolic reactions and it is quite possible, as demonstrated by Lyman and Barron (61),

for a tissue to be pathological and yet have a normal  $Q_{O_2}$ . These workers found that the average endogenous  $Q_{O_2}$  values of normal and nephritic kidneys were the same, although the oxidation of pyruvate and lactate were greatly reduced in the nephritic kidneys. Thus, fundamental changes in the enzyme make-up of a tissue can occur without altering the oxygen consumption. Previous diet and differences in substrate in which the  $Q_{O_2}$  is measured may greatly affect

TABLE I  
*Metabolic interrelationships during shock*

| PERIPHERAL TISSUE  | LIVER  | KIDNEY   | BLOOD  |
|--|--|--|--|
| Increased glucose utilization                            | Increased glyco-<br>genolysis<br>Decreased glyco-<br>genesis   |  | Fall in venous $O_2$<br>Rise in sugar<br>Fall in sugar when<br>glucose utilization<br>exceeds supply   |
| Increased lactic acid<br>production                      |  | Retention of organic<br>acids  | Rise in lactic acid  |
| Increased pyruvic and<br>alpha keto acid pro-<br>duction |  |  | Rise in pyruvic and<br>alpha keto acids<br>Fall in $CO_2$<br>Fall in pH  |
| Creatine phosphate<br>breakdown                          |  | Creatinuria post<br>shock  | Rise in creatine   |
| Adenosine triphos-<br>phate breakdown                    |  |  |  |
| Release of inorganic<br>phosphate                        | Release of inorganic<br>phosphate  | Phosphate retention  | Rise in phosphate  |
| Release of potassium                                     | Release of potassium   | Potassium retention  | Rise in potassium  |
| Protein breakdown<br>to polypeptides and<br>amino acids  | Protein breakdown<br>(?)<br><br>Decreased metabo-<br>lism of amino<br>acids and ammonia<br>Decreased urea pro-<br>duction<br><br>Decreased plasma<br>protein and pro-<br>thrombin syn-<br>thesis | Decreased excretion<br>of urea and NPN<br>compounds<br><br><br>Increased nitrogen<br>excretion post<br>shock | Rise in polypeptides<br>(?)<br><br>Rise in NPN, includ-<br>ing amino acids,<br>uric acid, creatine,<br>and ammonia<br><br>Fall in plasma pro-<br>teins |

the result. Furthermore, in the study of the enzymes and other constituents of a tissue, a change in concentration from the normal may not necessarily be of significance unless it can also be shown that the rate of turnover of the enzyme system is also abnormal or inadequate. The rate of turnover of an enzyme system may be quite independent of the absolute concentration of the enzyme at any one time.

Beecher and Craig (9) were the first to report studies on the metabolism

of isolated tissues from animals in hemorrhagic shock. They reported that neither the oxygen consumption nor the lactic acid output of brain cortex, heart muscle, kidney cortex or liver were significantly changed from normal in cats fasted sixteen hours and then subjected to hemorrhagic shock. Russell, Long and Wilhelmi (79), on the other hand, using twenty-four hour fasted rats and forty-eight hour fasted cats found a very considerable reduction in the  $Q_{O_2}$  of liver slices but little alteration in the  $Q_{O_2}$  of kidney during hemorrhagic shock. The differences found by the two groups of investigators in the response of the liver were apparently due to the effects of fasting, for Craig (18) later confirmed the findings of Russell and her associates on fasted rats and further showed that anoxia produces a much smaller change in the  $Q_{O_2}$  of livers from fed rats than in those from fasted ones. It is not known whether differences in the glycogen content of the livers or some other factors are responsible for the greater sensitivity to anoxia of the livers of fasted animals.

The nature of the defect in respiration of liver tissue during shock is not yet known. Russell, Long and Wilhelmi (79) suggest that one of the early effects may be a loss or disorganization of coenzyme factors essential for normal tissue functions. They found that hot water extracts of normal liver which contain the water soluble coenzymes, effected a definite improvement in the respiration when the  $Q_{O_2}$  was mildly depressed by shock, although it had no effect when the  $Q_{O_2}$  was moderately or severely reduced. Similar results were reported by Grieg (47), who in addition found evidence of damage to the protein part of the oxidative enzyme systems. Sodium succinate, a readily oxidizable substrate for normal tissue, produced a marked but temporary increase in the oxygen uptake of both normal liver and liver from bled rats. With 0.01 M succinate the increase in  $Q_{O_2}$  over the no-substrate level was the same for normal and pathological tissue indicating that it had not resulted in improvement or repair of the basal respiration of the liver from the shocked rats. When 0.04 M succinate was used there was a still greater increase in oxygen uptake. Furthermore, under these circumstances, the lower the basal  $Q_{O_2}$  during shock, the greater was the increment produced by the 0.04 M succinate. Since the rate of oxidation of succinate is greatly increased by mincing or homogenizing the tissue, this response may be an indication of increasing disorganization of liver tissue as shock progresses. This impression is borne out by unpublished observations by Darrow and Engel (20) on the electrolyte and water content of livers from shocked rats which indicate considerable tissue disorganization. Thus, although the succinoxidase system and the ability to take up oxygen and carry out the final steps of hydrogen and electron transport thereby appear to be intact in liver from shocked rats, there is no evidence that the increased oxygen uptake through this system is available to the tissues for energy to maintain function. This is of importance in view of the suggestion (57, 67) that succinate may be a useful therapeutic agent in shock.

Russell and her associates found the effects of hemorrhage upon the oxygen uptake of kidney cortex to be relatively slight, even after profound shock. With glucose as a substrate the respiration was better maintained during shock.

When kidney cortex from normal rats was subjected to anoxia *in vitro* for sixty minutes, its respiration was reduced to the same degree as liver treated similarly. However, glucose, which had no effect on the respiration of anoxic liver slice, nearly doubled the  $Q_{O_2}$  of the kidney tissue after sixty minutes of anoxia. The ready utilization of glucose by the anoxic kidney may be one factor in the greater ability of that organ to withstand the effects of anoxia during shock.

Govier, Greer and Grieg have published a series of reports on the blood and tissue concentrations of several of the B-complex vitamins in their free and combined forms during shock (40, 41, 42, 43, 46, 47, 48). As is well known, thiamine, nicotinamide and riboflavin when combined with certain other compounds constitute an important group of coenzymes whose presence in proper concentration and proportions is essential for the normal processes of metabolism. Thiamine combines with phosphate to form diphosphothiamine, or cocarboxylase. This coenzyme participates in a variety of metabolic reactions, among the best known of which are those concerned with the metabolism of pyruvic and other alpha-keto acids. Accumulation of pyruvic acid in the blood is a characteristic feature of thiamine deficiency. Govier and Greer, impressed by what they thought were similarities between shock and thiamine deficiency, such as elevated blood pyruvate, studied the effects of thiamine on hemorrhagic shock in dogs. They reported that thiamine increased the survival time, caused a rise in blood pressure and produced a delayed fall in blood pyruvate. Study of the plasma thiamine levels by Govier showed that those dogs having a high plasma thiamine level showed a greater resistance to shock by hemorrhage than those with low plasma thiamine. Dogs which went into shock with a small amount of bleeding showed an increase in plasma thiamine with the onset of shock, while the more resistant dogs showed no such rise. Fortifying the dogs with thiamine beforehand appeared to increase their resistance to hemorrhage somewhat, although it by no means prevented shock. Since thiamine must be in its phosphorylated form in order to function as the coenzyme cocarboxylase, the effect of hemorrhage on dephosphorylation of cocarboxylase in muscle, duodenum and liver was then studied by Govier and Grieg (43). They found that during shock and anoxia an actual dephosphorylation of cocarboxylase occurred, muscle and duodenum showing a greater degree of dephosphorylation than liver. Dogs which went into shock with a small amount of bleeding appeared to show a greater dephosphorylation than the more resistant dogs. Thiamine therapy resulted in a resynthesis of cocarboxylase, the latter often reaching concentrations greater than at the start of the experiment. *In vitro* experiments confirmed the fact that animal tissues break down cocarboxylase under anaerobic conditions and that cocarboxylase can be resynthesized from thiamine aerobically. Alexander (2) confirmed the breakdown of cocarboxylase in muscle in dogs during hemorrhagic shock, but in contrast to the findings of Govier and Grieg, reported an increase in free thiamine and cocarboxylase in the liver. The therapeutic claims of Govier and his associates have not yet been confirmed.

Similar results have been reported by Grieg for the coenzymes, cozymase



and alloxazine adenine dinucleotide, in the tissues during shock. Cozymase is an important coenzyme containing nicotinamide, while alloxazine adenine dinucleotide contains riboflavin. After hemorrhage in dogs the coenzyme content of brain, muscle and liver decreased in that order, the decreases in cozymase being more consistent than those in alloxazine adenine dinucleotide. Those dogs which developed shock with a small amount of bleeding showed a greater tendency to destruction of these coenzymes than did the more resistant animals. Therapy with nicotinamide and riboflavin resulted in restoration of the coenzyme concentrations, but no data are given as to the therapeutic value of these substances. Further work along these lines is indicated to determine the precise significance of coenzyme destruction during shock and to explore the value of vitamin therapy for shock.

#### ENDOCRINE FACTORS IN HOMEOSTASIS

The endocrine glands play an important rôle in the regulation of metabolic processes under normal and pathological conditions. This control is of great importance in maintaining biochemical homeostasis for the organism. Under conditions of stress such as shock, these homeostatic mechanisms are undoubtedly called into play. However, information on this subject is far from complete because, except for the adrenal medulla, the evidence for the participation of the endocrine glands in the metabolic processes of shock is largely indirect in the case of certain glands, and entirely unavailable in the case of others.

The emergency function of the adrenal medulla has long been known and emphasized through the work of Walter Cannon. The hemodynamic responses to sympathetic activity and epinephrine secretion during shock are clearly of the nature of homeostatic reactions to maintain the maximum blood flow to vital organs during the period of stress. The epinephrine hyperglycemia has likewise been considered a protective measure, although the precise reason for it was not well understood. The recent demonstration of greatly increased carbohydrate requirement by the tissues during shock explains the protective value of the epinephrine hyperglycemia.

There has been increasing evidence that the adrenal cortex, under the control of the adrenotropic hormone of the anterior pituitary gland, plays an important rôle in the body's resistance to shock and other forms of stress. The adrenalectomized animal and the patient with Addison's disease are notoriously sensitive to any shock-inducing procedures. The normal animal subjected to stress shows unmistakable signs of activation of the adrenal cortex. Donahue and Parkins (22) and others (81) have reported depletion of lipoid in the adrenal cortex of dogs during shock. We have shown that this is a much more rapid response than was generally supposed (30). Within an hour after hemorrhage in rats, lipoid depletion of the cortex could be demonstrated both histologically and by chemical determination of the cholesterol content of the glands. Sayers and his co-workers (81) in this laboratory have shown that lipoid depletion is indicative of activation of the adrenal cortex by the pituitary adrenotropic hormone and occurs under a wide variety of circumstances in which there is

presumably an increased requirement for adrenal cortical hormone. Twenty-four hours after a non-fatal hemorrhage we have found a statistically significant increase in the size of the adrenal glands of rats, further evidence of their increased activity (30). And finally, Weil and Browne (88) and Venning, Hoffman and Browne (87) have demonstrated in the urine of postoperative patients substances with the properties of the adrenal cortical steroids. Winter and his associates (81) have confirmed this in the case of burns, again suggesting an increased secretion of these hormones during stress. Despite these findings, however, it has not yet been possible to isolate any specific metabolic reaction attributable to adrenal cortical activity during shock. This is undoubtedly due to the fact the reactions initiated by shock so rapidly overshadow what compensatory processes may be set in motion by the anterior pituitary-adrenal cortex system that the latter become extremely difficult to detect. The adrenal cortical steroids have been shown to promote the retention of sodium, chloride, and water and the excretion of potassium, to increase the plasma volume, the blood pressure, and liver glycogen, to promote gluconeogenesis from protein or protein breakdown products, to decrease glucose utilization, and to increase plasma protein synthesis, all reactions which would be valuable in combating shock. From the evidence of activation of the glands it seems reasonable to suspect that these reactions may be taking place during shock even though they have not yet been demonstrated then. In view of the very close interrelationship between the hormones of the anterior pituitary, adrenal cortex, thyroid, pancreas, and gonads in controlling metabolism, further investigation is indicated on the behavior of these glands during shock.

#### DISCUSSION

The material reviewed represents only a small beginning of a large and complex problem. Much has been learned in the past few years, but even where progress has been made there are still many serious gaps in our knowledge. A variety of metabolic defects have been described, but it has not always been possible to determine which of these, either alone or in combination with others, represent critical disturbances and which are of minor significance. Different tissues and organs have been shown to be affected by shock at different rates and to varying degrees, but the relative significance for the ultimate outcome of partial or complete loss of organ function has not been clearly established. In the case of some tissues, data on their metabolic activity during shock are as yet very incomplete, so that a false impression of their importance may be given. Little has been reported on the metabolism of brain and nervous system or heart, tissues highly sensitive to oxygen lack, although work is in progress in several laboratories. This work is of great importance, for a demonstration of any serious metabolic breakdown in either the central or peripheral nervous system would do much to explain some of the characteristics of late shock.

One objective of this type of research has been to establish a rational basis for the therapy of the so-called "irreversible" stage of shock, that stage in which

the restoration of fluid and colloid is no longer effective in restoring the circulation. Profound anoxia is a prominent feature of this phase. As yet no entirely new method of therapy of proven value has been evolved. Based on the biochemical evidence, several types of adjuvants to the conventional therapy of shock have been suggested and are under investigation. These involve (a) attempts to correct abnormalities in the blood chemistry whose persistence may be considered as "perpetuating factors" in shock, (b) supplying nutritive substrates, (c) supplying components of enzyme systems known to be damaged and (d) use of hormones. . . . In the first group may be mentioned the revival of interest in the use of alkali. Cannon and others introduced alkali therapy by mouth and parenterally during the last war, but as the methods of blood transfusion and preservation were improved, alkali therapy was largely forgotten. Recent re-emphasis on acidosis in shock as a perpetuating factor has lead to a re-evaluation of this type of therapy. Fox (34) has reported encouraging results from the use of oral sodium lactate in burn shock in humans. Levine and his co-workers (57) describe a considerable reduction in mortality in dogs brought to the stage of "irreversible" shock by hemorrhage and treated with whole blood supplemented with sodium bicarbonate and glucose and with whole blood plus sodium lactate. In the second group, that of supplying nutritive substrates, little has been accomplished. Levine found that the addition of glucose to the whole blood and alkali gave somewhat better results than whole blood alone. Glucose, alone or with whole blood, has not been of particular value. Sodium succinate has been suggested by Mylon, de Sütö-Nagy and Winternitz (67) on the grounds that the succinate would be a readily utilizable substrate during anoxia and possibly would have a catalytic effect on tissue respiration as is suggested by *in vitro* work. However, Levine found that the beneficial effects of intravenous sodium succinate in shock are due to the sodium ion and the correction of the acidosis, for it is no more effective than sodium bicarbonate. The use of the various B-complex vitamins, thiamine, nicotinamide and riboflavin by Govier, Greer and Grieg represent the first attempts to restore coenzymes which are destroyed during shock. No adequately quantitative data are available yet to evaluate this type of therapy. Among hormones, the adrenal cortical steroids have been the subject of considerable interest. Despite some early enthusiastic reports there is no evidence at present that they possess any real value in the treatment of shock except in cases of adrenal insufficiency. Under normal circumstances the secretion of hormone by the adrenal cortex in response to stress is probably a very delicately balanced reaction which may actually be hindered by indiscriminate use of cortical hormone.

When shock has reached the so-called "irreversible" stage, a variety of complex disturbances have taken place or are set in motion, involving almost all levels of organization of the organism. It is unlikely, therefore, that any single therapeutic agent will be found capable of correcting these defects. A thorough understanding of these various disturbances and their ramifications will be needed before a rational plan of therapy can be worked out.

## BIBLIOGRAPHY

1. AGGOZZOTTI, G.: Chem. Abstr. 36: 4876, 1942.
2. ALEXANDER, B.: J. Clin. Investigation, 23: 259, 1944.
3. ALLISON, J. B., COLE, W. H., LEATHAM, J. H., NASTUK, W. L., AND ANDERSON, J. A.: J. Biol. Chem. 147: 255, 1943.
4. AUB, J. C.: Am. J. Physiol. 54: 388, 1920.
5. AUB, J. C. AND CUNNINGHAM, T. D.: Am. J. Physiol. 54: 408, 1920.
6. AUB, J. C. AND WU, H.: Am. J. Physiol. 54: 516, 1920.
7. BAETJER, A. M.: Am. J. Physiol. 112: 138, 1935.
8. BEARD, J. W. AND BLALOCK, A.: Arch. Surg. 22: 617, 1931.
9. BEECHER, H. K. AND CRAIG, F. N.: J. Biol. Chem. 148: 383, 1943.
10. BLALOCK, A. AND LEVY, S.: Am. J. Physiol. 118: 734, 1937.
11. BOLLMAN, J. L., MANN, F. C., AND MAGATH, T. B.: Am. J. Physiol. 69: 371, 1924.
12. BOLLMAN, J. L., MANN, F. C., AND MAGATH, T. B.: Am. J. Physiol. 78: 258, 1926.
13. BOLLMAN, J. L. AND FLOCK, E. V.: Am. J. Physiol. 142: 290, 1944.
14. BROFMAN, B. L. AND GREEN, H. L.: Fed. Proc. 2: 5, 1943.
15. BWATERS, E. G. L. AND POPJAK, G.: Surg. Gynec. & Obst. 75: 612, 1942.
16. CLARKE, A. P. W. AND CLEGHORN, R. A.: Endocrinology, 31: 597, 1942.
17. CLEGHORN, R. A. AND MCKELVEY, A. D.: Canad. J. Research 22: 12, 1944.
18. CRAIG, F. N.: J. Biol. Chem. 150: 209, 1943.
19. CUTHBERTSON, D. P.: Lancet, 1: 433, 1942.
20. DARROW, D. C. AND ENGEL, F. L.: Unpublished Observations.
21. DAVIDSON, E. C.: Arch. Surg. 13: 262, 1926.
22. DONAHUE, J. K. AND PARKINS, W. M.: Proc. Soc. Exper. Biol. & Med. 32: 1249, 1935.
23. DRURY, A. N.: Physiol. Rev. 16: 292, 1936.
24. DUNCAN, G. W.: Arch. Surg. 46: 214, 1943.
25. DUNPHY, J. E., GIBSON, J. G. AND KEALEY, J. L.: Surg. Gynec. & Obst. 72: 823, 1941.
26. DUVAL, P., ROUX, J. C. AND GOFFRON: Presse méd. 42: 1785, 1934.
27. EBERT, R. V., STEAD, E. A., WARREN, J. V., AND WATTS, W.: Am. J. Physiol. 136: 299, 1942.
28. ELMAN, R. AND LISCHER, C. E.: Ann. Surg. 118: 225, 1943.
29. ENDRES, G. AND NEUHAUS, C.: Ztschr. f. d. ges. exper. Med. 47: 585, 1925.
30. ENGEL, F. L.: Proc. Conf. on Factors Producing Adrenal Hypertrophy in Animals. New York. Josiah Macy, Jr. Foundation. 1942.
31. ENGEL, F. L., WINTON, M. G., AND LONG, C. N. H.: J. Exper. Med. 77: 397, 1943.
32. ENGEL, F. L., HARRISON, H. C., AND LONG, C. N. H.: J. Exper. Med. 79: 9, 1944.
33. FLEISCH, A.: Schweiz. med. Wchnschr. 68: 81, 1938.
34. FOX, C. L., JR.: J. A. M. A. 124: 207, 1944.
35. FRANK, H. A., AND FINE, J.: J. Clin. Investigation, 22: 305, 1943.
36. FRIEDEMANN, T. E., AND BARBORKA, C. T.: J. Biol. Chem. 141: 994, 1941.
37. GANGITANO, L.: Boll. Soc. Ital. Biol. Sper. 15: 444, 1940.
38. GELLHORN, E.: Autonomic Regulations. New York, Interscience, 1943.
39. GLENN, W. W. L., MUUS, J., AND DRINKER, C. K.: J. Clin. Investigation, 22: 451, 1943.
40. GOVIER, W. M.: J. Pharmacol. & Exper. Therap. 77: 40, 1943.
41. GOVIER, W. M. AND GREER, C. M.: J. Pharmacol. Exper. Therap. 72: 317, 1941.
42. GOVIER, W. M. AND GREER, C. M.: J. Pharmacol. Exper. Therap. 72: 321, 1941.
43. GOVIER, W. M. AND GRIEG, M. E.: J. Pharmacol. Exper. Therap. 79: 240, 1943.
44. GREEN, H. N.: Lancet, 245: 147, 1943.
45. GREEN, H. N. AND BIELSCHOWSKY, M.: Lancet, 245: 153, 1943.
46. GRIEG, M. E.: J. Pharmacol. Exper. Therap. 81: 164, 1944.
47. GRIEG, M. E.: J. Pharmacol. Exper. Therap. 81: 240, 1944.
48. GRIEG, M. E. AND GOVIER, W. M.: J. Pharmacol. Exper. Therap. 79: 169, 1943.
49. GRINDLEY, J. H., HERRICK, J. H., AND MANN, F. C.: Am. J. Physiol. 132: 489, 1941.
50. GUTMAN, H., KROLL, H. H., OLSEN, W. H., LEVINSON, S. O., AND NECHELES, H.: War Med. 1: 824, 1941.

51. HAIST, R. E., AND HAMILTON, J. J.: *J. Physiol.* 102:471, 1944.
52. HAWK, P. B., AND GIES, W. J.: *Am. J. Physiol.* 11:171, 1904.
53. HENDERSON, Y. L., PRINCE, A. L., AND HAGGARD, H. W.: *J. A. M. A.* 69:965, 1917.
54. HOAR, W. S., AND HAIST, R. E.: *J. Biol. Chem.* 154:331, 1944.
55. KERR, S. E.: *J. Biol. Chem.* 67:689, 1926.
56. LAUSON, H. D., BRADLEY, S. E., AND COURNAND, A.: *J. Clin. Investigation*, 23:381, 1944.
57. LEVINE, R., HUDDLESTON, B., PERSKY, H., AND SOSKIN, S.: *Am. J. Physiol.* 141:209, 1944.
58. LIPMANN, F.: *Advances in Enzymology*, 1:99, 1941.
59. LIPMANN, F.: *A Symposium on Respiratory Enzymes*. Wisconsin Univ. of Wisc. Press. 1942.
60. LURJE, A.: *Am. J. Surg.* 32:313, 1936.
61. LYMAN, C. M., AND BARRON, E. S. G.: *J. Biol. Chem.* 132:293, 1940.
62. MACLOED, J. J. R.: *Am. J. Physiol.* 55:184, 1921.
63. MANERY, J. F., AND SOLANDT, D. Y.: *Am. J. Physiol.* 138:499, 1943.
64. MANN, F. C.: *Quart. Bull. Ind. Univ. Med. Cen.* 4:43, 1942.
65. McMICHAEL, J.: *Quart. J. Exper. Physiol.* 27:73, 1938.
66. MIKHNEV, A. L.: *Klin. med.* 18:151, 1940.
67. MYLON, E., DE SÜTÖ-NAGY, G. J., AND WINTERNITZ, M. C.: Personal Communication.
68. MUIRHEAD, E. E., ASHWORTH, C. T., KREGEL, L. A., AND HILL, J. M.: *Arch. Surg.* 45:863, 1942.
69. NEUFFELD, A. H., TOBY, C. G., AND NOBLE, R. L.: *Proc. Soc. Exper. Biol. & Med.* 54:249, 1943.
70. NISHIMURA, S.: *Okayama Igakkai Zassi.* 53:1331, 1941.
71. PENNER, A., AND BERNHEIM, A.: *Arch. Path.* 30:465, 1940.
72. PHILLIPS, R., AND VAN SLYKE, D. D., quoted by Richards (75).
73. PRICE, P. B., HANLON, R. C., LONGMIRE, W. P., AND METCALF, W.: *Bull. Johns Hopkins Hosp.* 69:327, 1941.
74. REIN, H.: *Arch. f. klin. Chir.* 189:302, 1937.
75. RICHARDS, D. W.: *Bull. New York Acad. Med.* 20:463, 1944.
76. RIEGEL, C.: *J. Biol. Chem.* 74:123, 1927.
77. RUSSELL, J. A.: Unpublished Observations.
78. RUSSELL, J. A., LONG, C. N. H., AND ENGEL, F. L.: *J. Exper. Med.* 79:1, 1944.
79. RUSSELL, J. A., LONG, C. N. H., AND WILHELMI, A. E.: *J. Exper. Med.* 79:23, 1944.
80. RUSSELL, J. A., WILHELMI, A. E., AND ENGEL, F. L.: Unpublished Observations.
81. SAYERS, G., SAYERS, M. A., FRY, E. G., WHITE, A., AND LONG, C. N. H.: *Yale J. Biol. & Med.* 16:361, 1944.
82. STOLFI, G.: *Boll. Soc. Ital. Biol. Sper.* 15:457, 1940.
83. TAYLOR, A. E., AND LEWIS, H. B.: *J. Biol. Chem.* 22:71, 1915.
84. TAYLOR, F. H. L., LEVENSON, S. M., DAVIDSON, C. S., BROWDER, N. C., AND LUND, C. C.: *Ann. Surg.* 118:215, 1943.
85. TRUSLER, H. M., EGBERT, H. L., AND WILLIAMS, H. S.: *J. A. M. A.* 113:2207, 1939.
86. VAN SLYKE, D. D., AND MEYER, G. M.: *J. Biol. Chem.* 16:197, 1913.
87. VENNING, E. H., HOFFMAN, M. M., AND BROWNE, J. S. L.: *Endocrinology*, 35:49, 1944.
88. WEIL, P., AND BROWNE, J. S. L.: *J. Clin. Investigation*, 19:772, 1940.
89. WESTON, R. E., JANOTA, M., LEVINSON, S. O., AND NECHELES, H.: *Am. J. Physiol.* 138:450, 1943.
90. WILSON, W. C., AND STEWART, C. P.: *Edinburg M. J.* 46:153, 1939.
91. WINTER, H. A., GLENDENING, M. B., WILLIAMS, H. H., ABBOTT, W. E., HIRSCHFELD, J. W., AND HELLER, C. G.: *Endocrinology*, 35:224, 1944.
92. WOOD, G. O., MASON, M. F., AND BLALOCK, A.: *Surgery* 8:247, 1940.
93. ZIFF, K.: *Arch. f. exper. Path. u. Pharmacol.* 167:60, 1932.
94. ZWEMER, R., AND SCUDDER, J.: *Surgery*, 4:510, 1938.



## MECHANISMS OF FAINTING

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Fainting is an exceedingly common reaction, and there are few people who have not fainted or been close to fainting one or more times in their lives. In most instances it is without serious clinical implications. Occasionally, however, fainting may be the symptom of a more serious disorder, and certainly when fainting occurs repetitively it is always symptomatic of a significant structural or emotional disturbance. For this reason, and because fainting is so often confused with epilepsy by the clinician, understanding of the mechanisms and the correct differential diagnosis of fainting are of great importance.

My interest in the problem of fainting dates from House Staff days at The Mount Sinai Hospital. There the advice and encouragement of Dr. Moschowitz, on whose service many of the original observations to be reported here were made, stimulated a line of clinical investigations which has continued up to the present time and promises to extend well into the future. Subsequent association with the late Dr. Soma Weiss, whose extensive contributions to the subject of syncope represent almost the entire bulk of our current knowledge, marked a second period of great inspiration. In reporting original observations in this paper, I wish to acknowledge the collaboration of my colleagues, Drs. Sydney Margolin and Frank Engel at The Mount Sinai Hospital, and Drs. John Romano, Eugene B. Ferris, Jr. and T. McLin at the Peter Bent Brigham Hospital, and the Cincinnati General Hospital.

At the outset, certain terms should be clarified. Fainting, or syncope, generally refers to a transient reaction terminated by brief loss of consciousness in which there is decrease in the tone of the postural muscles and falling. Since unconsciousness is usually implied when one speaks of syncope or fainting, the terms syncopal reaction or fainting reaction are used when referring to the symptom complex when it terminates before loss of consciousness has resulted. As is well known, in many types of fainting, unconsciousness may be forestalled by assuming the recumbent position. Patients may deny fainting because they have never actually lost consciousness, yet may have experienced all the symptoms leading up to unconsciousness, which they prevent by lowering the head or lying down. The terms used by most patients to describe their syncopal experience include giddiness, light-headedness, dizziness, "graying-out," "black-ing-out," spots before the eyes, faintness, etc. The physician frequently uses the term vertigo in referring to these symptoms. This is incorrect. The term, vertigo, should be restricted to the sensation of rotation of self or environment, which is a symptom of disturbance of the vestibular mechanism, and not a symptom of syncope.

It should also be pointed out that the clinical picture of syncope may be modified by the character and severity of incidental pre-existent structural

defects. Thus, elderly patients with cerebral arteriosclerotic changes may be expected to lose consciousness quicker and to recover more slowly. Similarly, such patients are more likely to show focal neurological signs during and following syncope. Convulsive movements, usually clonic twitches, may be anticipated in any patient with syncope who is unconscious long enough (more than 10–15 seconds), but they will develop sooner in patients with pre-existent cerebral disease. It is rare for a true grand-mal seizure, with tonic and clonic phases, to be a complication of syncope. Indeed, we have provoked syncope in known epileptics without ever inducing a true epileptic fit.

#### CLASSIFICATION

The following classification is based upon the major pathophysiologic disturbance involved. Each type will be discussed in detail.

- A. Fainting related to fall in blood pressure in the erect position.
  - 1. Vasodepressor syncope.
  - 2. Chronic orthostatic hypotension.
- B. Fainting related to cardiac asystole.
- C. Fainting related to local changes in cerebral blood flow.
- D. Fainting related to paroxysmal changes in cardiac rhythm.
- E. Fainting related to obstruction of blood flow from the left ventricle.
- F. Fainting related to anoxemia.
- G. Fainting related to acapnia.
- H. Hysterical fainting.

#### *A. Fainting related to fall in blood pressure in the erect position*

Fall in blood pressure in the erect position constitutes by far the most common mechanism of syncope. Two important categories may be described: vasodepressor syncope, and chronic orthostatic hypotension. The clinical picture of the faint, however, is essentially the same in both categories. This type of syncope characteristically occurs in the erect and rarely in the recumbent position. The symptoms are quickly relieved by assuming the recumbent position, in milder cases even by simply lowering the head, but may recur promptly when the erect position is resumed. The earliest symptom is weakness, most marked about the legs, followed by nausea, sweating, sighing, respiration, yawning, restlessness, and pallor. These symptoms may last from one to five minutes, and may be relieved by assuming the recumbent posture. Otherwise, they are followed by light-headedness, blurring of vision, unconsciousness, and falling. If the patient is maintained in the erect position, loss of consciousness may be followed in 15 to 30 seconds by convulsive movements. During the period of developing symptoms the blood pressure is falling, but unconsciousness does not result until systolic pressure has fallen below 80 mm. Hg. Pulse may accelerate or slow, and just preceding loss of consciousness, varying degrees of heart block may develop. Because of this last feature, some investigators have referred to instances of this type of syncope as "vasovagal syncope." This is not a good term, since it has been frequently demonstrated that atropine will block this

vagal element of the reaction without preventing syncope. In the recumbent position, blood pressure usually rises promptly, pulse returns to normal, there is flushing of the face, and return of consciousness, although nausea and sweating may continue for several minutes.

It is obvious that in this type of fainting the primary defect relates to a disturbance in the blood pressure regulating mechanism in the erect position (1). To effect the return of blood to the heart against the force of gravity, certain compensatory mechanisms come into play. These probably involve venous tone, muscle tonus, arteriolar tone, and perhaps certain shunting mechanisms, but the relative importance of each of these has yet to be determined. Most of the symptoms and signs preceding the loss of consciousness are the expression of the compensatory devices utilized to overcome the postural defect, *i.e.*, pallor, sighing, yawning, restlessness, vagal overactivity, etc. The actual loss of consciousness relates to two major factors: diminished cardiac output and insufficient systolic pressure to raise the column of blood from the heart to the brain. The unconsciousness is thus an expression of acute cerebral anemia. This is attested to by the electroencephalogram, which invariably reveals high voltage 2 to 4 per second waves at the point of loss of consciousness, but no change during the premonitory phase. Figure 1 illustrates the typical electroencephalogram, blood pressure and pulse changes during an instance of this type of syncope; in this case, vasodepressor syncope.

The major points differentiating syncope relating to falling blood pressure from other types are the relation to posture and the premonitory period of 1 to 5 minutes preceding the actual loss of consciousness. The etiology of this type of fainting will be elucidated further in the discussion of the subgroups that follows:

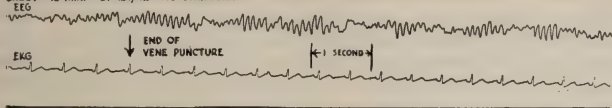
*Vasodepressor Syncope.* It is convenient to subdivide vasodepressor syncope into two categories, one in which reflex or psychological factors play a dominant role and a second, in which structural factors leading to an acute disproportion between blood volume and the size of the vascular bed, play the major role. This subdivision is not meant to represent a strict bipolar classification, but rather emphasizes the two extremes in the etiology of a more or less homogeneous syndrome in which psychological, reflex, and structural factors play roles of varying importance. From the point of view of therapy an evaluation of the importance of each of these factors is essential.

The first type, in which psychologic and reflex factors play the dominant role is an acute reaction occurring under conditions of real or fantasied injury or threat of mutilation in persons whose postural reactions immediately before were normal. It is the reaction seen so frequently following venepuncture, minor surgical procedures and minor injury, upon viewing mutilation, autopsies, operation, etc., upon hearing bad news, and sometimes it follows no perceptible or demonstrable stimulus. It is frequently a "first-time" phenomenon, repetitive exposure to the same provocative stimuli seeming to "immunize" the individual against recurrence of the reaction. This learning process has recently been evaluated in a more or less quantitative fashion during the exposure of 78

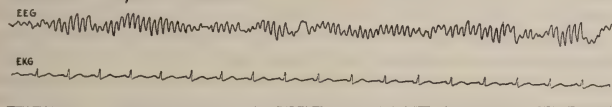
male University students to altitudes of 35,000 to 38,000 feet in a decompression chamber. In spite of a sustained incidence of decompression sickness in the

#### 1B. VASODEPRESSOR SYNCOPÉ

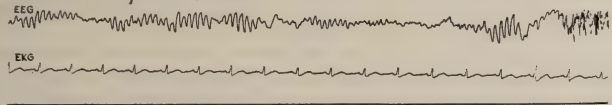
ERECT 15 MIN. BP 124/92 NO SYMPTOMS



ONE MINUTE BP 112/90 NO SYMPTOMS



TWO MINUTES BP 100/70 WEAK, SIGHING



THREE MINUTES WEAK, SWEATING, PALE, NAUSEATED

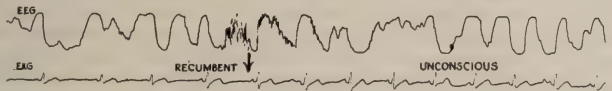
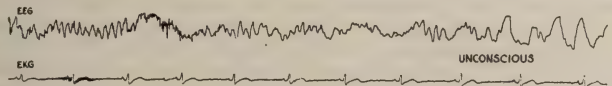
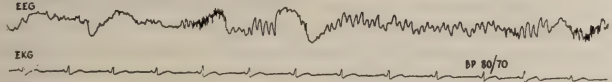


FIG. 1. Vasodepressor syncope following venepuncture. Premonitory symptoms of weakness, sighing, sweating, pallor, nausea, and falling blood pressure last 1 to 2 minutes. The E.E.G. shows high voltage slow waves appearing simultaneously with loss of consciousness, but insignificant changes during the premonitory period.

group, the incidence of vasodepressor syncopal reactions fell from 18 per cent on the first flight to 2 per cent on the seventh flight (2).

Except for some rare types to be mentioned below, efforts to establish any simple sensory modality or afferent pathway for the initiation of the reaction have failed (1). We have provoked vasodepressor syncope experimentally by venepuncture, arterial puncture, by distension of duodenum, colon, rectum, and vagina, and by induction of mild disturbances in consciousness, but usually a second attempt to provoke the reaction by the same stimulus is unsuccessful. Pain, in the same individual, may on one occasion provoke vasodepressor syncope, and on a second occasion abort it (1). Obviously, psychological factors play an important role in this type of vasodepressor syncope. Whether vasodepressor syncope develops in a given setting appears to be dependent upon many variables including the nature of the person, the nature of the setting, the individual's preparation for the noxious stimulus, his capacity to diffuse individual anxiety through such means as identification with a group, the specific nature of the ego defenses used previously, and the acuity and intensity of the noxious stimulus (3). The greater the severity of the noxious stimulus in terms of tissue injury, the less important psychological factors become in the genesis of the faint. With severe enough injury, any person may experience vasodepressor syncope regardless of previous ego strength. It represents a physiological mode of retreat from the noxious agent. In such catastrophic conditions as acute pancreatitis, perforation of a viscus, or acute myocardial infarction, the reaction is likely to be sustained and then no longer should be classified as syncope, but rather as acute circulatory collapse or shock, depending upon the intensity.

When vasodepressor syncope occurs repeatedly, either following minor noxious stimuli or without obvious provocation, in a person with no evidence of any organic disorder which leads to postural fainting, it is usually indicative of a serious neurotic disturbance. Essentially, it represents a vegetative neurotic symptom complex in which certain disturbances in circulatory dynamics occur concomitantly with emotions of fear and anxiety, which overwhelm the ego and lead to a flight marked by weakness, falling, and loss of consciousness (sham death?) (3). While we are not yet prepared to outline definitively the configurational personality structure or more specific conflict situations in vasodepressor syncope, a few observations seem pertinent. Neurotically determined vasodepressor syncope is more common in men, especially in men characterized by considerable narcissistic consideration of their bodies. Any cut, bruise, injury, however trivial it may be, appears to mobilize an exaggerated degree of castration anxiety. Usually there has been considerable attention to the body and pride in muscle mass and athletic endeavor. It is of interest in this regard, that the few women with repetitive vasodepressor syncope we have studied, have revealed many dominant masculine traits. The essential differences between neurotically determined vasodepressor syncope and hysterical syncope will be pointed out in a subsequent section.

There are a few rare types of vasodepressor syncope in which reflex factors play a dominant role while psychological factors are of little importance. Most important of these is reflex carotid sinus hypersensitivity of the depressor type. Instances in which a marked fall in blood pressure and no asystole occur on



stimulation of the carotid sinus are rare. We have observed only one such case in more than fifty examples of syncope provoked by carotid sinus stimulation. More often vagal and depressor types are mixed and after atropinization the fall in blood pressure is not sufficient to provoke symptoms. So far, this is the only purely reflex type of vasodepressor syncope we have encountered. Rarely, disease of the brain stem may lead to episodes of vasodepressor syncope. It has been seen during pneumoencephalography and in patients with posterior fossa neoplasm. Drs. Eugene B. Ferris, Jr. and Charles Aring recently told me of a 72 year old physician who had had a number of episodes of typical vasodepressor syncope, with fall in blood pressure, sweating, and bradycardia during the course of a year. After his last attack, he developed progressive neurological signs and finally quadriplegia and died two days later. Postmortem examination revealed a sclerotic plaque almost completely occluding the basilar artery and fresh thrombus at the point of stenosis. Periodic alterations in blood flow to the brain stem probably accounted for this patient's syncope. These instances of pure reflex or neurogenic vasodepressor syncope are exceedingly rare, however, and usually present associated signs or symptoms that lead to the correct diagnosis.

The precise means by which the sudden disturbance in circulatory dynamics is brought about in these types of vasodepressor syncope has not yet been clarified. We suspect that a reflex change in muscle tonus may play an important role and that phylogenetically the reaction bears some relationship to the phenomenon of sham death in animals, but this hypothesis has not yet been subjected to rigid scrutiny. Splanchnic pooling and venous pooling in the lower extremities have also been suggested. Once initiated, the disturbance may last hours after the noxious stimulus has been withdrawn, the blood pressure falling and symptoms recurring each time the person attempts to stand up. Most often, however, recovery is a matter of minutes.

At the other end of the etiologic spectrum are examples of vasodepressor syncope which are always symptomatic of an underlying and more or less acute structural or physiologic disorder, and which disappear as soon as the underlying disturbance is corrected. The provocative factors which lead to this type of syncope are those which result in an acute disparity between the size of the vascular bed and the circulating blood volume or those which acutely disrupt the normal postural regulating mechanisms. The patient is generally asymptomatic in the recumbent position, but experiences rapid fall in blood pressure and syncopal symptoms when standing. Obviously, if the derangement is extreme enough, evidences of collapse become apparent even in the recumbent position, and then one is dealing with acute circulatory collapse or shock. Often syncope is the first symptom of the underlying disorder, the nature of which is revealed rather promptly on examination. In contrast to the patients with vasodepressor syncope in which psychological or reflex factors play the dominant role and who usually recover rather promptly from their faint and are able to go about their business, these patients often show continued, and sometimes progressive evidence of being ill, even though their postural maladaptation may

be compensated for. The common causes of this type of syncope are as follows: *Hemorrhage*, both external and internal, often is complicated by syncope. With external bleeding psychological factors may play a greater role. The first symptom of gastrointestinal bleeding often is fainting. A common story of patients with bleeding duodenal ulcer is that they developed weakness, pallor, sweating, nausea, and finally faint while on the toilet passing a tarry stool. Obviously the bleeding had occurred sometime earlier, and the combination of the motionless, semi-erect posture and the obstruction of venous return during straining in the presence of reduced blood volume leads to fall in blood pressure and syncope. *Fever*, particularly when of sudden onset, with the associated flushing and shunting of blood to the skin, may lead to a relative enlargement of the vascular bed. Before this has been compensated for by increase in plasma volume, assumption of the erect position may be accompanied by marked fall in blood pressure and fainting, due to inadequate filling of the blood bed and inadequate return of blood to the right heart. This is a not uncommon occurrence even during benign, but acute infections like grippe, tonsillitis, etc., and patients should be warned of the danger of jumping out of bed and standing motionless. The fainting seen during motionless standing in *hot environments* or after *strenuous exercise* results from similar enlargement of the vascular bed. *Acute dehydration*, from severe vomiting, diarrhea or sweating may reduce plasma volume acutely enough to lead to fainting in the erect position. *Prolonged recumbency*, particularly in debilitated persons, often results in a decrease in the efficiency of the mechanism regulating blood pressure upon change in posture. The factors involved are not well understood, but it is this disturbance that accounts for the fall in blood pressure and fainting of patients getting out of bed for the first time or sitting upright on the bed-pan. By exercise in bed and care in arising, this disturbance is usually promptly overcome. *Certain drugs*, notably sodium nitrite, nitroglycerine, amyl nitrite, and magnesium sulfate in excessive dosage induce fainting in the erect position through their effect on the peripheral circulation. Exposure to volatile organic nitrite compounds in industry may be the source of epidemics of syncope. Curare may induce postural syncope by its effect on muscle tonus. *Pregnancy* may in the early months be associated with marked postural maladaptation. The exact mechanism is unknown. Because of the nausea during the period of falling blood pressure upon arising in the morning, this syndrome may be confused with the usual nausea of early pregnancy. We have observed patients whose postural maladaptation has disappeared after a few weeks, but whose morning nausea continued, so the two are probably unrelated. *Post-infection*: after a number of infections, notably influenza and infectious mononucleosis, postural hypotension may develop and may persist for weeks. The reasons for this are not known, but it obviously involves more than the effects of prolonged recumbency.

*Chronic Orthostatic Hypotension*. As the term indicates this is a chronic form of postural maladaptation in which syncopal symptoms or actual syncope occur each time the patient attempts motionless standing. The postural maladaptation is extremely resistant to therapy and once initiated it may persist indefi-

nately. In the literature this syndrome is referred to as "orthostatic hypotension," "postural hypotension," and "orthostatic circulatory insufficiency." We have added the adjective chronic to distinguish it from vasodepressor syncope which is also a postural syncope but which is usually more or less self-limited.

The syndrome occurs most often in middle-aged or elderly patients, and is commonly related to structural damage to the neural pathways concerned with the reflex control of blood flow on change in posture. Thus, it is seen in patients with tabes dorsalis and other diseases of the spinal cord, peripheral neuritis, and in patients with evidences of disturbances in the sympathetic nervous system (4). It is also seen in Addison's disease, where the already low blood pressure may fall to syncopal levels on motionless standing and rarely in patients with large varicosities or other venous anomalies of the lower extremities (5).

In chronic orthostatic hypotension the association between the erect posture and the syncopal symptoms is usually very obvious to the patient, and hence the diagnosis is readily made. The patient notes symptoms soon after arising in the morning and in severe cases becomes bed-ridden. In milder instances the patient may be more or less free of symptoms when active, but may become faint while shaving, standing at a stove, etc. When examined on a tilt-table the fall in blood pressure when tilted erect is usually very rapid and profound. In milder cases the marked fall in systolic pressure may be preceded by a period of narrowing pulse pressure (rising diastolic and falling systolic pressures) and increasing tachycardia lasting 8 to 15 minutes. The Valsalva maneuver (straining against closed glottis or blowing against positive pressure) will promptly provoke syncope at this stage. The unconsciousness is always accompanied by high voltage slow waves in the electroencephalogram.

Increasing tissue pressure in the lower portion of the body may lessen the fall in blood pressure. Stead (4) has demonstrated that the fall in blood pressure may be prevented by standing the patient in water up to the nipple-level. Spingarn and Hitzig (6) have diminished the fall in blood pressure temporarily by the use of desoxycorticosterone acetate and sodium chloride in quantities sufficient to produce a small amount of dependent edema. After several weeks the beneficial effects were lost. MacLean (7) has had some success by having the patient sleep with the bed elevated to an angle of 20 to 25° particularly when a small amount of edema of the feet accumulated. The use of sympathicomimetic drugs like ephedrine, benzedrine, paredrine, and paredrinol, is of some benefit in the mild but not effective in the more pronounced cases.

#### *B. Fainting related to cardiac asystole*

This is the second most common mechanism of fainting. Clinically this is a sudden faint and may be distinguished from the faint due to falling blood pressure by the absence of the premonitory symptoms. Loss of consciousness is preceded only by a second or two of light-headedness. Recovery of consciousness is equally abrupt and occasionally the patient will be unaware of the fleeting loss of consciousness or say: "I must have dropped off to sleep for a second." The unpleasant symptoms of nausea and sweating are usually absent or insignif-

icant. The relationship between the development of symptoms and posture depends upon the duration of the cardiac standstill. Unconsciousness develops in the standing position with asystole of 4 to 8 seconds, in the sitting position with asystole of 8 to 12 seconds, and in the recumbent position with asystole longer than 12 seconds. During the syncope the patients show marked pallor of the face, and pulse and blood pressure cannot be obtained. Hyperpnea is a common associated symptom. With loss of consciousness of more than 1 to 2 seconds' duration the electroencephalogram reveals high voltage slow waves which last until consciousness is recovered (1). This is illustrated in Figure 2. With no change in consciousness and with only fleeting light-headedness, the electroencephalogram will show little or no change (1). The loss of consciousness is obviously related to the failure of blood to reach the brain during the period of asystole. If the period of cerebral anemia is sufficiently prolonged, convulsive movements may appear. Usually these consist of clonic movements, but when asystole lasts longer than 30 seconds a rather severe convulsion may develop.

Cardiac arrest may result from disease of the conduction system of the heart, it may be of reflex origin, or may result from a combination of both. Reflex cardiac standstill is by far the more common. The efferents of the reflex arc are the vagus nerves. The right vagus nerve supplies the S-A node and stimulation leads to inhibition of the auricular beat. The left vagus nerve is distributed chiefly to the A-V bundle and stimulation leads to varying degrees of auricular-ventricular block. With reflex stimulation either or both mechanisms may be involved. The afferents of the vagal reflex arc, all of which synapse in the brain stem, are widely distributed, and include the carotid sinus, aortic sinus, eye (oculocardiac reflex), and various portions of the gastrointestinal, genito-urinary, and respiratory tracts. This wide distribution of afferent sites for the vagal reflex arc suggests that disease in many portions of the body may lead to sensitization of the vagal reflex arc and hence to potential cardiac standstill. This is indeed true, but, fortunately, this sensitization only infrequently leads to spontaneous clinical symptoms. In all types of reflex vagal overactivity, atropine, through its action in blocking parasympathetic impulses, is a specific drug and is of great value in diagnosis.

*Carotid Sinus Reflex Hypersensitivity (Cardio-inhibitory type).* This is the most common type of reflex vagal overactivity leading to asystole and syncope. The afferent impulse is mediated through a branch of the glosso-pharyngeal (IX) nerve. As part of the essential mechanism for the control of circulation, particularly to the head, it is not surprising that it should be readily influenced by disease or drugs involving the reflex arc directly or indirectly. Sigler (9), in a group of 1886 patients between 10 and 85 years of age, was able to provoke asystole of 3 seconds or longer by massage of the carotid sinus in 18 per cent. In 81 patients chosen among consecutive hospital admissions, we found a positive reaction in 19 per cent (10). Obviously then, the ability to produce asystole by massage of the carotid sinus does not establish that to be the etiology of spontaneous syncope. The diagnosis of syncope due to carotid sinus reflex

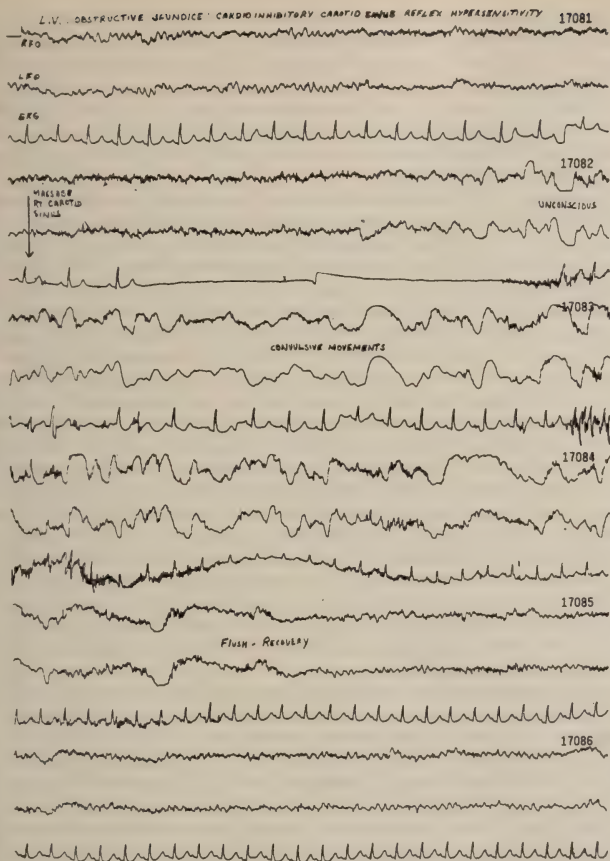


FIG. 2. Cardioinhibitory carotid sinus reflex syncope. With an asystole of 8 seconds there was complete loss of consciousness with falling, followed by clonic movements. The E.E.G. showed high voltage slow waves during the period of unconsciousness.

hypersensitivity of the cardio-inhibitory type is only warranted if the following criteria are satisfied: (1) the loss of consciousness is sudden, with minimal premonitory symptoms; (2) asystole of sufficient duration to produce changes in



consciousness can be produced by massage of the carotid sinus; (3) spontaneous attacks do not occur when sufficient atropine or ephedrine has been given to prevent bradycardia on manual stimulation. If spontaneous attacks occur in association with pressure on the neck by the collar, upon turning of the head, or during other maneuvers that lead to local stimulation, the diagnosis is aided. When these criteria are satisfied it will be found that there are relatively few patients experiencing spontaneous syncope as a result of a hypersensitive carotid sinus reflex of the vagal type.

Sensitization of the carotid sinus reflex arc may result from disease of any portion of the reflex arc or of other vagal afferents. Hypersensitivity may be associated with local disease involving any portion of the reflex arc, *i.e.*, around the carotid sinus, such as arteriosclerosis of the carotid artery, and neoplastic or inflammatory masses in the neck; neuritis or other processes involving the glossopharyngeal or vagus nerves; disease of the brain stem involving the vagus nucleus; myocardial disease, notably coronary artery disease, acute rheumatic carditis, and toxic myocardoses (9, 11). In addition, disease of other afferents to the vagus center lower the threshold to carotid sinus stimulation. This has been clearly demonstrated in biliary tract disease, where in a group of 23 patients with more or less acute disease of the gall bladder or bile ducts, 18 or 78 per cent showed a hypersensitivity of the carotid sinus vagal reflex arc (10). Seven of these patients had had spontaneous syncopal symptoms. A similar summation effect has been seen in a patient with renal colic (and syncope), a patient with glaucoma, and in an instance of distension of the duodenum by balloon (1). Certain drugs, notably digitalis, may also sensitize the reflex arc. The demonstration of overactivity of the vagal reflex arc, taken in conjunction with the associated clinical signs and symptoms may thus prove valuable not only in the understanding of certain spontaneous syncopal reactions, but also in the differential diagnosis of the underlying condition. For example, the incidence of vagal carotid sinus reflex hypersensitivity is high in obstructive jaundice, but low in jaundice due to hepatitis (10).

It is not possible to know how often syncope results from acute disease involving vagal afferents other than the carotid sinus. Rarely a chronic reflex reaction is encountered. Weiss and Ferris (12) reported a patient with a traction diverticulum of the esophagus in whom the passage of a bolus of food invariably led to cardiac standstill and fainting. Atropine prevented the reaction. They also have reported a patient with a sensitive area of the posterior pharynx, touching of which led to cardiac standstill and fainting. Iglauer (13) reported a case in which dilatation of a stenosed cardia (cardiospasm) caused cardiac standstill. These types of reflex vaso-vagal syncope are rare, but should be readily diagnosed.

*Stokes-Adams Syndrome* is the eponym applied to the syncope resulting from asystole in the course of heart block due to organic involvement of the conduction system. The attacks of asystole are likely to be long, often exceeding a minute in duration, and the syncopal experience is often complicated by convulsions. Between attacks the pulse is slow and the electrocardiogram reveals evidence of heart block as well as other evidences of myocardial damage. Stokes-Adams

syndrome is readily distinguished from the reflex types of heart block, but the superimposition of reflex factors should not be overlooked. Thus atropine, by eliminating reflex stimulation of the vagus, may occasionally reduce the number of spontaneous attacks. Ephedrine and related drugs are also of value if the myocardium is not too severely involved.

### *C. Fainting related to local changes in cerebral blood flow*

*The cerebral type of carotid sinus reflex hypersensitivity* is the most important example of this mechanism. Ferris, Capps, and Weiss (11) in their original description of carotid sinus syncope, distinguished three types, vagal (cardiac standstill), depressor, and cerebral. The first two types have already been discussed. In the cerebral type stimulation of the carotid sinus led to unconsciousness and frequently focal neurological signs without significant change in pulse or blood pressure. These investigators were very careful to establish the specificity of the carotid sinus in the reaction. This they did by massaging other portions of the neck and shoulder and by occluding each carotid artery without provoking syncope as well as by local anesthesia of the carotid sinus. Subsequent investigators have been careless in this respect, resulting in confusion with hysterical syncope, some instances of which may be provoked by massage of many portions of the body, including the neck. This differentiation will be discussed further in the section on hysterical fainting.

Clinically, the cerebral type of carotid sinus syncope is characterized by abrupt fainting which is often accompanied by focal neurological signs, as focal convulsions, mono- or hemiparesis, paresthesias, aphasia, etc. The focal neurological signs are predominantly those of cortical involvement and they may occur in any posture, but are more common in the sitting or standing positions. The development of symptoms is usually related to movements that result in stretching of/or pressure on the carotid sinus. During the faint, in addition to the focal neurological manifestations, there may be pallor or flushing of the face, hyperpnea, but no significant change in pulse or blood pressure. Frequently two, and even three, types of carotid sinus reflex hypersensitivity occur together. The cerebral component may be identified by stimulating the carotid sinus after atropinization, which eliminates the vagal element, and by following the blood pressure during stimulation in the recumbent position, which minimizes the depressor element. During the period of unconsciousness the electroencephalogram reveals high voltage slow waves arising diffusely. When focal neurological manifestations of cortical origin develop without unconsciousness, the electroencephalogram reveals slow waves arising from the cortex contralateral to the signs and on the same side as the stimulated carotid sinus (1). Neither symptoms nor electroencephalographic changes result when the carotid artery is occluded below the carotid sinus. This is illustrated in Figure 3. In our experience (1, 3, 14), diffuse or focal slowing of the electroencephalogram has been an invariable finding in the cerebral type of carotid sinus syncope. All the cases we have seen diagnosed as such, which failed to show slowing, either had very fleeting (less than 1 to 2 seconds' duration) and minor changes in consciousness

GE. AGE 29 CAROTID SINUS REFLEX HYPERSENSITIVITY, CEREBRAL TYPE.

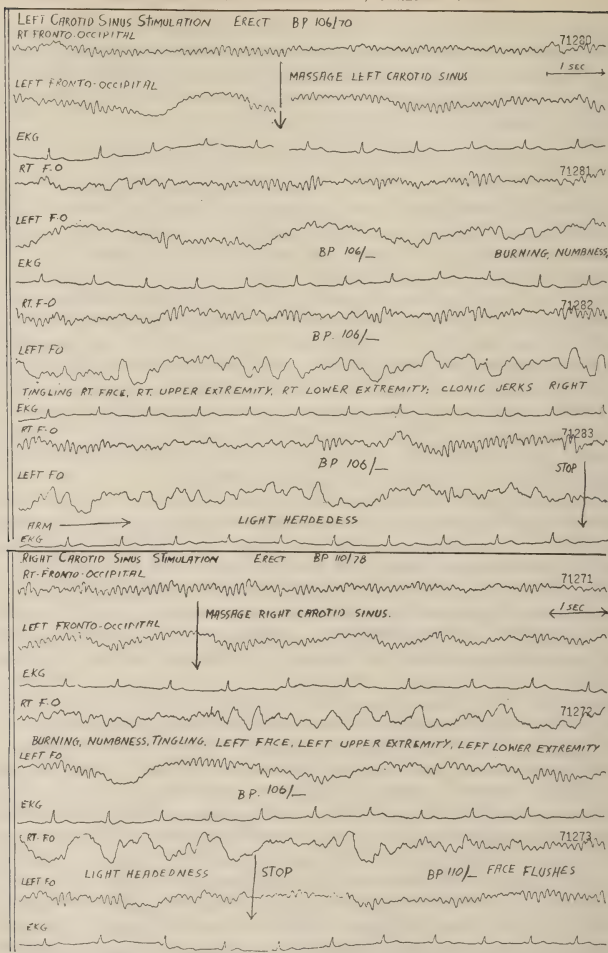


FIG. 3. Cerebral type of carotid sinus reflex hypersensitivity. Stimulation results in slow waves in the E.E.G. from the ipsilateral cortex and sensory and motor symptoms of the contralateral face, arm and leg. There were no significant changes in pulse and blood pressure.

and showed slow waves when unconsciousness was more prolonged, or they were cases of hysterical syncope in which stimulation of many other portions of the body was equally effective in provoking syncope.

The mechanism of this type of syncope has not yet been conclusively demonstrated. The character of the focal neurological manifestations and the focal electroencephalographic changes, the undoubted evidence of cerebrovascular disease in many of these patients, and the fact that the carotid sinus mechanisms are so intimately concerned with the regulation of cerebral circulation, all lead us to the view that the symptoms result from reflex constriction of cerebral arteries. Ferris, Capps, and Weiss (9), using relatively crude methods, were unable to detect any gross changes in cerebral blood flow, but admittedly were unable to rule out focal changes. They noted, however, that during the induced attacks, the cerebrospinal fluid pressure dramatically fell and the pulsations diminished and that during recovery the pressure temporarily rose above normal and the pulsations widened. As an alternate possibility they suggested a direct reflex to the mid-brain involving centers concerned with consciousness. It may be that there are several mechanisms involved.

*Local Cerebral Disease* may rarely be associated with sudden loss of consciousness of brief enough duration to be classified as syncope. Syncopal symptoms, as fleeting light-headedness, dizziness, etc., may also occur. This is seen particularly in patients with *hypertension* and with advanced cerebral *arteriosclerosis*, sometimes as a prodrome to thromboses. It is a rare occurrence in *brain tumor*. Rarely it may occur as a prodromal symptom of *migraine*. The mechanism, in all likelihood, is one of sudden reduction of blood flow through involved blood vessels, perhaps due to spasm. Any transient focal neurological sign may accompany such a reaction. The diagnosis is difficult and is made by excluding the other types of syncope and establishing the presence of the underlying structural disorder.

Any of the above types of syncope due to changes in local cerebral blood flow may be followed by vasodepressor syncope. This is primarily a psychological reaction on which the impending or threatening loss of consciousness acts as a provoking stimulus. We have witnessed this a number of times in tense and anxious individuals in whom the induction of early symptoms of cerebral carotid sinus reflex syncope was followed several minutes later by the typical changes of vasodepressor syncope even though the electroencephalogram had already returned to normal. This reaction was usually accompanied by evidences that the experience had provoked considerable apprehension. As with most other provocateurs to vasodepressor syncope this was less likely to happen on a second occasion.

#### *D. Fainting related to paroxysmal changes in cardiac rate or rhythm (other than asystole)*

Rarely fainting occurs at the onset of a paroxysmal tachycardia. This has been thought probably to result from a transient, acute fall in cardiac output with resultant cerebral anemia. Comean (15), however, has recently demon-

strated complete cardiac arrest between the cessation of normal rhythm and the establishment of auricular fibrillation in a patient whose attacks of fibrillation were generally ushered in by syncope. Sometimes the symptoms associated with the onset of paroxysmal tachycardia may provoke sufficient anxiety to precipitate an attack of vasodepressor syncope.

#### E. *Fainting related to obstruction of flow from the left ventricle*

This is a presumptive mechanism, as its occurrence has never actually been proven. The fainting seen in patients with *aortic stenosis* may possibly result from such mechanical obstruction. The usual story of syncope in aortic stenosis is that the loss of consciousness occurs abruptly during exertion, and may be aborted by standing still. This suggests the possibility of a disparity between cardiac output and tissue needs due to the mechanical obstruction of outflow. The possibility of a reflex from the aortic arch cannot be overlooked, and it is well known that in such patients the carotid sinus is frequently sensitive to mechanical stimulation. In *dissecting aneurysm* of the aorta, obstruction of flow to the brain, particularly if the mouths of the carotid arteries and subclavian arteries are involved, may contribute to the syncope which is often the presenting symptom. Vagal reflexes from the aortic arch may also play a role.

#### F. *Fainting related to anoxemia*

Sudden reduction in the oxygen saturation of the arterial blood may lead to disturbances in the level of awareness and sudden unconsciousness. (Loss of consciousness of normal people exposed to atmospheres of low oxygen tension will not be considered here.) Clinically it is rather rare. We have reported one case, and cited another from the literature, of fainting in a patient with *congenital heart disease* (Tetralogy of Fallot) (14). This patient, who was only very slightly cyanotic at rest, would become extremely cyanotic and lose consciousness under any circumstance where increased cardiac output was required, particularly physical exertion. The electroencephalogram, after the patient walked 30 steps, showed high voltage slow waves. The patient was bed-ridden because of this symptom. Patients with *chronic pulmonary disease*, i.e., pulmonary fibrosis, emphysema, etc. and some patients with congestive heart failure, who already have some degree arterial oxygen unsaturation may become dizzy and lose consciousness during exertion or during exposure to rarified atmospheres (aeroplane or mountain trips). The increase in anoxemia probably accounts for this.

The characteristic physical signs of the underlying disease usually provide the clue to these less common syncopal reactions.

In most instances the direct effects of the anoxia on the central nervous system result in the disturbances in consciousness and syncope. Occasionally anoxia results in vasodepressor syncope.

#### G. *Fainting related to acapnia*

Vigorous overventilation, with the resultant blowing off of carbon dioxide, reduction of arterial carbon dioxide tension, and rise in arterial pH leads to reduc-



tion in the level of awareness in all normal people after 2 to 3 minutes. This is associated with numbness and tingling, particularly of face and hands, fullness in the head, tinnitus, and floating sensations, and it is accompanied by the appearance of slow waves in the electroencephalogram. The patients, however, do not fall. The disturbance in consciousness and slowing of the electroencephalogram both are greater in the presence of low blood sugar and the erect posture; conversely, high blood sugar and the recumbent posture reduce the intensity of the reaction (16). If hyperventilation is continued for longer periods tetany results. It is our opinion that the disturbance in consciousness and the tetany are unrelated phenomena. Each may occur in the absence of the other. The disturbance in consciousness appears to be related to a combination of decrease in cerebral blood flow and a change in the oxygen requirements of the cerebral tissue, leading essentially to a relative hypoxia (17).

Hyperventilation is a common neurotic symptom. It may occur as an hysterical symptom or may accompany the emotions of fear, rage, or anxiety. The symptoms, as we have outlined them, are not those of syncope as defined in this paper because the patients do not fall. Indeed, the disturbance in consciousness may often be detected only by direct testing and it may be followed by amnesia. However, hyperventilation may provoke true syncope by at least four different mechanisms: (a) The subjective symptoms, with the sense of impending loss of consciousness, may provoke vasodepressor syncope in anxious patients by the mechanisms already described. (b) Hyperventilation in the erect position is always associated with some decrease in systolic blood pressure, decreased pulse pressure, and tachycardia. In patients who have a tendency toward orthostatic hypotension, this additional burden may prove the "last straw." (c) The apnea seen after hyperventilation may rarely be accompanied by reflex cardiac standstill. (d) Hyperventilation may provoke hysterical fainting in susceptible individuals.

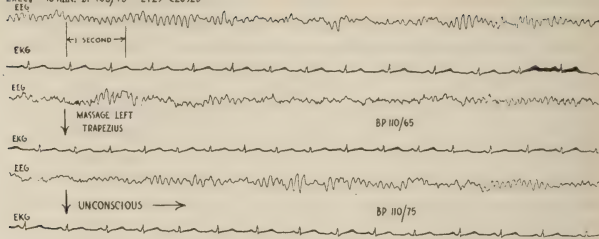
Thus, while hyperventilation *per se* does not result in syncope, it may occasionally precipitate syncope indirectly. Since hyperventilation is used by many physicians to provoke epileptic (*petit mal*) seizures, these alternate possibilities must also be kept in mind.

#### H. *Hysterical fainting*

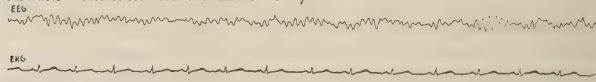
Hysterical syncope is an important variety of neurotically determined fainting which is to be contrasted with vasodepressor syncope. In the discussion of the latter type of syncope we pointed out that it represented a vegetative neurotic symptom in which certain disturbances in circulatory dynamics occur concomitantly with emotions of fear and anxiety which overwhelm the ego and lead to a flight marked by weakness, falling, and loss of consciousness. In contrast, hysterical fainting appears to be the substitutive or symbolic expression of an emotion, an attempt at a partial relief of the chronic unrelieved emotional tension in which loss of consciousness is not related to any demonstrable disturbance in the circulation or metabolism of the brain. A more detailed discussion of these two fundamental psychologic mechanisms as they relate to syncope will be found in another report (3).

## E.F. HYSTERICAL SYNCOPES

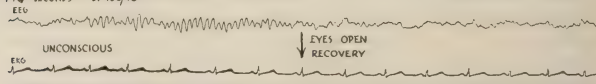
ERECT 13 MIN. BP 105/75 EYES CLOSED



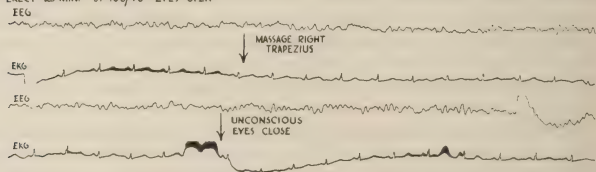
ONE MINUTE. UNCONSCIOUS - DOES NOT RESPOND BP 110/75



140 SECONDS BP 100/70



ERECT 23 MIN. BP 100/75 EYES OPEN



70 SECONDS BP 110/75

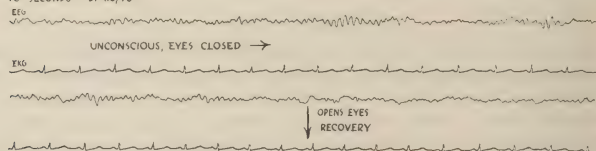


Fig. 4. Hysterical syncope: Fainting followed massage of the left trapezius but was unassociated with any change in E.E.G., pulse, blood pressure, or skin color. When the syncope was induced while patient's eyes were open, the eyes closed at onset of unconsciousness and alpha rhythm reappeared. Unconsciousness was marked by loss of muscle tone, falling, and lack of response to sensory stimuli.

Clinically hysterical fainting tends to occur more frequently among women. The patients often exhibit other hysterical manifestations and often manifest

little concern about their frequent faints ("la belle indifference"). Fainting is likely to occur in the presence of others. The loss of consciousness is usually abrupt and dramatic and is not preceded by premonitory symptoms. Although the patient falls or slumps to the ground, injury is infrequent. During the faint no changes in color, pulse, blood pressure, or respiration are noted and sweating does not occur. Consciousness is not regained upon attaining the recumbent position. The patient may remain unconscious for an indefinite period, ranging from a few seconds to hours. During the period of unconsciousness, regardless of its duration, there are no changes in the electroencephalogram. This is of the greatest importance in differential diagnosis for in all the other types of syncope so far described, in which the change in consciousness results ultimately from cerebral hypoxia, the electroencephalogram always shows marked changes if unconsciousness is complete and lasts more than 1 to 2 seconds. The electroencephalogram in hysterical syncope is illustrated in Figure 4. It will be noted in the second half of the record that when the faint was provoked with the patient's eyes open that she closed them during the faint and the electroencephalogram showed return of alpha rhythm.

Consistent with the hysterical character of this type of fainting it is usually quite easy to provoke syncope by manipulation of almost any portion of the body, particularly with the aid of suggestion. For this reason, as has already been mentioned, confusion with the cerebral type of carotid sinus syncope is quite easy if areas other than the carotid sinus are not also manipulated.

#### DISCUSSION

A word might be said about the relative incidence of the various types of syncope. Fall in blood pressure, cardiac standstill, local changes in cerebral blood flow, and hysteria probably account for 99 per cent or more of all instances of fainting. Of the individual types, vasodepressor syncope is by far the most common, particularly when one considers that it is a type of fainting almost taken for granted. Ahronheim (18) recorded 127 instances of vasodepressor syncopal reactions among 1,000 consecutive air cadets following withdrawal of blood for a Kahn test. The total number of vasodepressor syncopal reactions in the course of selective service examinations and at Blood Donor Centers in the past 4 years staggers the imagination. The remaining types occur with sufficient frequency to be important clinically, but are relatively rare compared to vasodepressor syncope. While hypersensitivity of the carotid sinus reflex can be demonstrated in a high percentage of patients the occurrence of spontaneous syncope by this mechanism is relatively uncommon.

The correct diagnosis of the syncopal reaction can usually be made after careful history and physical examination. In obtaining a history, special attention should be directed toward: (a) frequency of the faint, (b) position in which the faint occurs, (c) nature of the provocative stimulus, which may include psychological data, (d) the occurrence, nature, and duration of symptoms preceding the loss of consciousness, (e) the duration of unconsciousness, (f) occurrence of focal neurological symptoms, (g) the speed of recovery and its relationship to

posture, (h) occurrence of tongue biting and incontinence, and, if possible, (i) an observer's account as to whether pallor, sweating, changes in pulse, or convulsive movements occurred. These historical data plus a specific history and a physical examination to reveal structural defects of importance, will yield the necessary information for the correct diagnosis in most cases. In patients in whom repeated fainting is the presenting symptom, we have devised a technique of examination which will elucidate the mechanism of fainting in most instances. It requires the use of a tilt-table and a 3-channel electroencephalogram. Two channels are used to record bipolar tracing from left and right fronto-occipital electrodes and one channel to record the electrocardiogram. The routine is as follows:

1. In the recumbent position 5 minute recordings of the electroencephalogram, the electrocardiogram and blood pressure at 1 minute intervals.
  2. In the recumbent position, vigorous hyperventilation for 3 minutes, recordings of the electroencephalogram, the electrocardiogram and blood pressure, and clinical symptoms including level of awareness.
  3. Rest for 10 minutes; occasional blood pressure recordings.
  4. Tilt up to 75° quickly, recording electroencephalogram and electrocardiogram during the change in position, and blood pressure readings as quickly as possible.
  5. Motionless standing for 15 minutes, recording blood pressure, electroencephalogram and electrocardiogram at 1 minute intervals, or continuously if symptoms develop.
  6. Stimulate first right, then left carotid sinuses, recording electroencephalogram, electrocardiogram, and blood pressure.
- If there is a reaction:
- (a) Occlude first the right, then the left carotid artery below the carotid sinus.
  - (b) Massage other portions of the neck and shoulder.
  - (c) If necessary, repeat the latter in the recumbent position and after gr. 1/50 of atropine intravenously.
7. After a short rest period, still erect, hyperventilate vigorously for 3 minutes, recording as before.
  8. Motionless standing for 5 minutes after hyperventilation.
  9. Venepuncture with dull needle and minimal reassurance.

We have utilized this technique in our investigations of syncope and have found it possible to precipitate syncope in the great majority of patients suffering from spontaneous syncopal symptoms. It is usually possible to establish whether the syncope so provoked is the same as the spontaneous syncope. Ordinarily the clinical data alone are sufficient to establish the nature of the spontaneous syncope. Occasionally the clinical history indicates that special procedures, such as introduction of a balloon into gastrointestinal tract, exercise, etc. be included. The continuous recording of pulse, blood pressure, electrocardiogram, and electroencephalogram plus clinical observations as to color, sweating, etc. provide all the criteria to establish the correct diagnosis.

The electroencephalogram, of course, also helps to rule out epilepsy, since the differentiation between fits and faints may occasionally be difficult. Most often the differential diagnosis is not difficult if a careful history is obtained, with special reference to the points already outlined which relate specifically to syncope.

## SUMMARY

Fainting has been classified on the basis of mechanisms as follows:

- A. Fainting related to fall in blood pressure in the erect position.
  1. Vasodepressor syncope.
  2. Chronic orthostatic hypotension.
- B. Fainting related to cardiac asystole.
- C. Fainting related to local changes in cerebral blood flow.
- D. Fainting related to paroxysmal changes in cardiac rhythm.
- E. Fainting related to obstruction of blood flow from the left ventricle.
- F. Fainting related to anoxemia.
- G. Fainting related to acapnia.
- H. Hysterical fainting.

The clinical differentiation between these types of syncope is discussed and a technique for the examination of patients with syncope is presented.

## REFERENCES

1. ENGEL, G. L., ROMANO, J., AND McLIN, T. R.: Vasodepressor and carotid sinus syncope: Clinical, electroencephalographic, and electrocardiographic observations. *Arch. Int. Med.*, 74: 100, 1944.
2. ROMANO, J., ENGEL, G. L., WEBB, J. P., FERRIS, E. B., RYDER, H. W., BLANKENHORN, M. A.: Syncopal reactions during simulated exposure to high altitude in decompression chamber. *War Medicine*, 4: 475, 1943.
3. ROMANO, J., AND ENGEL, G. L.: Studies of Syncope. The differentiation between vasodepressor and hysterical fainting. *Psychosomatic Medicine*, 7: 3, 1945.
4. STEAD, E. A. AND EBERT, R. V.: Postural Hypotension. A disease of the sympathetic nervous system. *Arch. Int. Med.*, 67: 546, 1941.
5. CHAPMAN, E. M., AND ASMUSSEN, E.: On the occurrence of dyspnoea, dizziness, and precordial distress occasioned by the pooling of blood in varicose veins. *J. Clin. Investigation*, 21: 393, 1942.
6. SPINGARN, C. L., AND HITZIG, W. M.: Orthostatic circulatory insufficiency: Its occurrence in tabes dorsalis and Addison's disease. *Arch. Int. Med.*, 69: 23, 1942.
7. MACLEAN, A. R., ALLEN, E. V., AND WAGATH, T. B.: Orthostatic tachycardia and orthostatic hypotension. Defects in venous return to the heart. *Am. Heart J.*, 27: 145, 1944.
8. SIGLER, L. H.: Hyperactive cardioinhibitory. Carotid sinus reflex: A possible aid in the diagnosis of coronary disease. *Arch. Int. Med.*, 67: 177, 1941.
9. ENGEL, G. L., AND ENGEL, F. L.: The significance of the carotid sinus reflex in biliary tract disease. *New England J. Med.*, 227: 470, 1942.
10. FERRIS, E. B., JR., CAPPS, R. B., AND WEISS, S.: Carotid sinus syncope and its bearing on the mechanism of the unconscious state and convulsions. *Medicine*, 14: 377, 1935.
11. WEISS, S., AND FERRIS, E. B., JR.: Adams-Stokes syndrome with transient complete heart block of vagovagal reflex origin. *Arch. Int. Med.*, 54: 931, 1934.



12. IGLAUER, S., AND SCHWARTZ, B. A.: Heart block periodically induced by the swallowing of food in a patient with cardiospasm (vagovagal syncope). *Ann. Otol. Rhin., & Laryng.*, 45: 875, 1936.
13. ENGEL, G. L., AND MARGOLIN, S. G.: Neuropsychiatric Disturbances in Internal Disease: Metabolic factors and electroencephalographic correlation. *Arch. Int. Med.*, 70: 236, 1942.
14. COMEAU, W. J.: The mechanism of syncopal attacks associated with paroxysmal auricular fibrillation. *New England J. Med.*, 227: 134, 1942.
15. ENGEL, G. L., ROMANO, J., FERRIS, E. B., JR., WEBB, J. P., AND STEVENS, C. D.: A simple method of determining frequency spectra in the E.E.G.: Observations on physiological variations in glucose, oxygen, posture, acid-base balance on the normal E.E.G. *Arch. Neurol. & Psychiat.*, 51: 341, 1944.
16. FERRIS, E. B., JR., RYDER, H. W., AND MOLLE, W.: Unpublished data.
17. ARONHEIM, J. H.: Emotional albuminuria. *War Med.*, 5: 267, 1944.

## ON THE RELATION OF THE THYROID TO ALLERGIC STATES

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It is not the intention of this brief communication to intrude upon the highly specialized field of allergy. Its object is merely to record some experiences in hospital and private practice which indicate the necessity of greater circumspection in the analysis of "allergic" cases, in order to ascertain the basic and accessory factors which enter into their composition. The subject is not new, but one which requires reiteration. The final diagnosis and treatment often lie outside the field of the allergist's endeavors.

The following is a striking example: In January of 1919 a young married woman was referred to me for a metabolic study. Her complaint was asthma of six years' duration which was growing progressively worse. She had gone from specialist to specialist, both here and abroad, and all sorts of tests and treatments were applied without permanent effect. Occasionally change of climate or location gave relief for a brief period. The reasons for improvement during these intervals will become clear later on.

The problem was obviously one of etiology and not diagnosis. The physical findings were clear cut, and pointed to bronchial asthma. The antecedent history relative to the respiratory tract revealed that the patient had had a nasal operation thirteen years before, and that she was subject to attacks of tonsillitis. She was regarded as definitely allergic, but the particular agent which provoked the attacks could not be ascertained from her history.

In order to carry out the purpose for which she was referred to me I suggested a complete metabolic study. The patient complained of being nervous at the time (she had grown to dread visits to doctors) and asked to have the examination postponed. This was agreed upon for a few days later, but the appointment was eventually cancelled.

On the Sunday following, I received a call from the patient's husband stating that she was suffering from a severe paroxysm of asthma. When I arrived the picture which the patient presented was classical. She was indigo blue and struggling for breath. The administration of the customary remedies gave her relief. She was familiar with this treatment and though grateful for the relief obtained, she did not return to the office for further examination.

On the following Sunday the paroxysm of asthma recurred and I was summoned again. The same palliative treatment was applied, with the warning that unless she would have the examination completed there would be no further visits from me. When she finally came I informed her that there was no need for further medical examination. Her case was obvious. Her worst paroxysms apparently occurred only on Sundays when her husband spent the day at home.

Briefly, this was not a sex problem, but one due to cultural incompatibility. Her husband, she believed, did not come up to her level. She was an intelligent woman, and when I explained the reasons for her difficulty, she agreed to change her attitude toward her husband. There were no further asthmatic attacks.

In retracing her history, I discovered that change of climate and location were beneficial in the past only when the husband did not accompany her.

The recovery from asthma was complete. Six years later she underwent an appendectomy under ether anesthesia and made an uneventful recovery. Ten years later she succumbed to a generalized carcinomatosis of ovarian origin.

In retrospect one could infer that this case was psychosomatic in its evolution.

This case is unique only in the prompt therapeutic response resulting from the elucidation of the provocative cause. What organic substrate was involved remains obscure—unless we regard the ovarian malignancy, which terminated the life of the patient ten years later, as a factor. In this connection it is interesting to note that Fishberg (1918) drew attention to the association of thyroid and ovarian dysfunction in an asthmatic, and Widal, Abrami and Gennes (1922) also recounted a case where asthma appeared to have been related to this type of dysfunction.

From the allergists point of view the explanation of the above case might be somewhat as follows: Allergic persons (and it is assumed that the persons in question are allergic) especially those with asthma and urticaria appear to have hyperirritability or instability of a portion of the autonomic nervous system.

An asthmatic patient is frequently designated as a vagotonic individual; the vagus system appears overactive and is not always held in check by the sympathetic. Spasm of the bronchial muscles results. Moreover, not only is the vagus system too active, but it is hyperreactive to stimulation. A stimulus which would be without effect in a normal person, it is stated, will be followed by a vagotonic response with resulting asthma in an allergic patient. This is described as the "trigger" mechanism.

The nerve-reacting mechanism seems "cocked ready to shoot," in the asthmatic person. Once one has developed the asthmatic state, and the autonomic nervous system has become hyperresponsive, the "trigger mechanism" is at work, and any of a variety of impulses may produce an attack of asthma. The contact with an "allergen" is *not* always essential. Anything that will throw the vagus into activity will cause trouble. Irritating gases, indigestion, shock, fright, sudden temperature changes, head colds, and the like will cause asthma under such circumstances.

It is further stated that the "trigger mechanism" can be set in cases where there is no specific sensitization to an allergen, at least none that can be demonstrated. This, it is claimed, explains some of the cases in which positive evidence of allergic sensitization is lacking.

The concept of "trigger action," however does not elucidate the underlying mechanism of the reaction, nor the precise reason for its evolution. It merely suggests the path along which, or through which, a certain reaction may take place. That the autonomic nervous system participates in the expression of allergic phenomena cannot be denied. It appears to regulate the type of reaction between stimuli and tissue reactivity. But what is back of the tissue reactivity?

Heredity is frequently considered as a factor in allergic conditions. Sporadic mention has been made of the relation of the endocrine system to allergic

diseases and cases are on record in which dysfunction of the thyroid gland has been found to play an important part. Moncorge (1900) and Ley (1910) noted the coupling of asthma with thyroid dysfunction. Levi and Rothschild (1911) advanced the theory of an endocrine origin, not only for asthma, but for spasmodic coryza as well. They based their assumption on the frequent improvement in some of these cases on thyroid therapy. Widal and Abrami (1924) discussed four cases in which exophthalmic goitre was associated with asthmatic spasms; and Elliot (1929) described five cases of hyperthyroidism and one of hypothyroidism each of which was associated with asthma. Two were relieved of their asthma and hyperthyroidism by thyroidectomy, and clearing up of definite focal infections. Iodine had a beneficial effect on the one case which was continuously hypothyroid.

It seems to me that the difficulty encountered in evaluating an allergic case arises from the customary approach to the problem. The allergic response is regarded as the dominant factor and not as the end-point of a series of biologic reactions. The order should be reversed. The endocrines should be placed first; the autonomic nervous system as the intermediate and tissue reactivity as the final link in the chain. By this method of analysis the true etiologic factor may be discovered and the effects of both hyper- and hypo-activity of a gland can be more readily understood.

It is recognized, of course, that functional disturbances in one part of the endocrine system may lead to, or result in, disturbances in other parts of the system. But the commonest endocrine dysfunctions which are associated with allergic states and which can be detected clinically, are related to the thyroid gland.

The cases selected for presentation belong to this group. All received the customary palliative and prophylactic allergic treatment, yet they proved refractory to such treatment.

*Case 1. History:* T. N., aged 13 years, was referred to me in April 1928 suffering from Grave's disease, the first signs of which had become manifest six months before. The basal metabolism was plus 61 per cent and the clinical findings were in keeping with the diagnosis. The interest of this case lies in the earlier history, in her family antecedents and in the ultimate therapeutic result.

In addition to a number of diseases of early childhood, the patient was subject to asthmatic seizure since infancy, and adrenalin was used repeatedly for the relief of the paroxysms.

Her family history was particularly impressive. The father was a neurotic individual who suffered from a bowel condition (mucous colitis?). He later became a pronounced psychopath. The mother was a highly emotional individual, subject to attacks of migraine, and showed both clinical and laboratory evidence of hyperthyroidism. One younger sister also had hyperthyroidism with confirmatory laboratory findings.

From the standpoint of heredity, therefore, the patient had all the prerequisites for the development of an allergic state, but the dominant feature amongst the hereditary stigmata was the tendency to hyperthyroidism. The exact relationship of this tendency to the asthma could not be considered certain until a thyroidectomy was performed. Thereby the Grave's disease was controlled and the asthma completely abolished.

*Case 2. History:* A married woman, aged 52 years, developed asthma directly after the onset of the climacterium. As all the other members of the family were known to me, I can state with certainty that they were all exempt from any allergic manifestations. The outstanding characteristic of the family was obesity, and the patient's mother had diabetes.

At the age of 32, the patient underwent a nephrectomy for a calculous pyonephrosis. She remained well up to the time of the climacterium. In general the physical findings were negative. Of the laboratory findings two points stood out, namely an elevated lipid content in the blood, and a tendency to a continuous alkaline tide in the urine. The significance of these findings was not fully understood at the time; however lipoidemia is often encountered in the climacterium. Subsequent tests for allergy were negative. Some reaction to bacterial antigens was obtained—but not sufficient to point to a specific etiology. Notwithstanding numerous consultations, the asthma proved refractory to all forms of treatment, and became so intractable that the patient was confined to bed continuously. The cough was constant, extremely exhausting, and was accompanied by the expectoration of large amounts of thick viscid mucus. As adrenalin became ineffective, the patient developed a narcotic addiction. She was bedridden for eleven years.

Domestic conditions were not of the best, and as they appeared to contribute to the distress of the patient, she was finally removed to a nearby resort. She remained there but a few days, when it was reported that she had developed congestive heart failure. She was brought back immediately by ambulance.

When I saw the patient again, I was amazed to find her suffering with acute hyperthyroidism with cardiac manifestations. Intensive lugolization was immediately instituted. The change that took place in the patient's condition, even within the first twenty-four hours, was remarkable.

The interest in this case does not reside in the fact that the Lugol's solution controlled the symptoms of hyperthyroidism, but the associated beneficial effect upon the asthma. Lugolization was continued until not only the symptoms of hyperthyroidism were fully controlled, but the asthma was completely relieved. The narcotic habit was also checked and the patient resumed a normal life.

Many years have elapsed since this episode and no major asthmatic attacks have developed in the interval. Minor attacks followed emotional upsets, at which times iodine was promptly effective. She finally died of a coronary artery occlusion at the age of 72.

The importance of this case is to be found largely in the question of the relation of the thyroid to the production of the malady. There was nothing in her previous history preceding the major thyroid crisis which could inculcate the thyroid as a factor in the causation of asthma. Two questions arise at this point. "Did a latent hyperthyroidism exist prior to this crisis which did not manifest itself by any of the criteria to which we are accustomed? Secondly, did it bear any relation to the asthma?"

Subsequent experience with a variety of so-called allergic conditions, such as asthma, hay-fever, urticaria and mucous colitis, with and without specific skin reactions, lead me to answer both these postulates in the affirmative. Close inquiry and accurate analysis often reveal the fact that thyroid dysfunction plays an integral part in these conditions.

*Case 3. History:* M. S., aged 30 years, who had an appendectomy at the age of 13, a tonsillectomy at 24, a salpingectomy and oophorectomy at the age of 26, had attacks of asthma of three years' duration. A head cold characterized by rhinorrhea, tearing of the eyes and sneezing initiated the present attack. After several months of having a "head cold," the patient stated that it spread to her chest and since then she has had spells of coughing and constant wheezing. After one month in bed, she took quinine one night; this was



followed the next morning by severe hives! Later that day her asthma became very much more severe and she received her first injection of adrenalin. Since then she had been hospitalized and under observation at the asthma clinics of three hospitals without any improvement.

The patient was admitted to the Hospital for Joint Diseases on March 10, 1935, after having been in a 'status asthmaticus' for the past four months during which time she received three or four injections of adrenalin a day and supplementary morphine. She had lost thirty five pounds in weight, vomited after the intake of food, was severely constipated, had headaches, extreme weakness and inability to walk. During severe attacks in the past year, she had occasional blood streaked sputum. The menses were regular.

*Examination:* On admission to the hospital, she was pale, sallow, breathing with difficulty, wheezing loudly so that it could be heard several feet from the bed, and so exhausted even talking for a moment fatigued her. The chest was full of râles of all kinds. The heart sounds were faint, obscured by the wheezes. The heart did not seem increased in size; the blood pressure was 160 systolic and 80 diastolic; the abdomen was negative and there was no adenopathy.

Abstracts from the previous hospitals were obtained. That of one hospital showed a gastrointestinal x-ray series to have been done without any significant findings. The second hospital reported a possible left maxillary sinusitis; while the third institution reported a moderate reaction to corn and orris root: the findings were otherwise negative.

*Course:* After several days during which adrenalin, morphine and glucose were given without any marked relief, studies were made on the blood chemistry which showed a cholesterol of 136, phosphorus of 2.3, and a normal calcium. Five drops of Lugol's solution were administered three times a day. In a short time, a noticeable improvement was apparent in the patient's asthmatic state. Two weeks after Lugol's solution was started the blood cholesterol showed a rise to 196, twelve days later a third cholesterol reading was 206. At the time of the third cholesterol determination, the patient's asthma had so markedly improved that it was possible to do a basal metabolism which was minus 12 per cent. All other laboratory tests were negative, including the blood count, serology, blood chemistry and urinalysis. A skin eruption was reported by the dermatologists to be due to iodine. The Lugol's solution was continued in spite of this and after a period of several weeks, the eruption definitely improved. The patient was admitted with a weight of 102 lbs. which rapidly decreased to 96 lbs., at which time Lugol's solution was started. Associated with the improvement in her asthmatic state, the weight showed a rapid and progressive increase until, at the time of discharge, May 4, 1935, the weight was 106 lbs.

She has been followed regularly in the Out-Patient Department. Since admission and upon the last examination on October 26, 1935, she had continued to improve. The weight at that time had increased to 129 lbs. and she had been free of asthma except for occasional wheezing. The eruption was much less marked. No other abnormal signs were elicited.

The above cases are cited as instances of the association of asthma with hyperthyroidism and the effect of treatment directed to the thyroid upon the asthma.

In my own experience, asthma is more frequently associated with hyper- than with hypothyroidism. Another type of allergic reaction in the presence of hyperthyroidism is manifested in intestinal disturbances (mucous colitis?). The following case is an example.

*Case 4. History:* A. R., aged 21 years was referred to me by his father (a physician) in 1929 suffering from what appeared to be colitis. The family history was negative except that the father suffered from a similar complaint but to a lesser degree.

The patient had had most of the diseases of early childhood including a streptococcus infection of the throat with endocardial involvement. He had pneumonia at 14 years of age and scarlet fever at 16.

His complaint at the time was a bowel disturbance of several years duration with frequent bouts of diarrhea alternating with constipation. He was found to be sensitive to milk. During these attacks, he showed anorexia, decrease in weight, headaches and dizziness.

*Examination:* The patient was of the asthenic type. He had a palpable thyroid, a slight VonGraefe and a tremor of the fingers. The basal metabolic rate was plus 23 per cent. The rest of the examination, including a barium enema, was negative.

On the assumption that as a background of the allergic disturbance there was a hyperthyroid factor, lugolization was instituted with complete relief of the symptoms.

Borderline cases, presenting features of both hyper- and hypothyroidism are not uncommon, and if any allergic condition is coexistent, therapy directed to the one or the other dysfunction, or a combination of the two, may effect a cure.

There are, however, certain types of allergic conditions which appear to be more specifically associated with hypothyroidism. Amongst these are urticaria, hay-fever, and angioneurotic edema. With regard to urticaria, many writers insist that sufferers frequently show manifestations of hypothyroidism and that they derive benefit from thyroid therapy. Others, however, note urticaria associated with hyperthyroidism which disappears when treatment for this condition is instituted. I am inclined to the view that hypothyroidism is by far the more frequent offender.

If we consider hypothyroidism as one of the features of lipoid nephrosis, it is significant that so many of these cases give a history of urticaria (sometimes giant urticaria) antecedent to the symptoms of nephrosis. Hay fever is another condition which frequently forms part of the history of nephrosis. Be that as it may, the association of hay-fever with hypothyroidism is not at all uncommon. The following three cases are illustrative of this point.

*Case 5.* (Courtesy of Dr. J. J. Vorzimer) *History:* Male, aged 34 years, came under observation in May 1940. A presumptive diagnosis of hypothyroidism was made based upon the symptoms of fatigue, dryness of the skin, frequent upper respiratory infections, which upon examination by a nose and throat specialist were found to be due to an allergic condition frequently seen in hypothyroidism. The diagnosis was confirmed when the basal metabolic rate was found to be minus 34 per cent, and cholesterol 312 mgs. per 100 cc. The patient was placed on thyroid therapy, taking as much as 4 gr. with definite clinical improvement.

In November, 1940, his basal metabolism rose to plus 26 per cent; cholesterol was 166 mg. per 100 cc.; pulse, 84; the blood pressure, 132 systolic and 80 diastolic. His nasal congestion had disappeared and there was no further evidence of allergic rhinitis.

*Case 6.* (Courtesy of Dr. J. J. Vorzimer.) *History:* Female, aged 8 years. Chief complaints: obesity, severe constipation, bowel movements only with enemata, sluggishness, dullness at school and dry skin. In addition there was a prolonged history of asthma and hay fever.

*Examination:* 52½ inches in height, weight, 82 lbs., hemoglobin, 70 per cent, blood pressure, 80 systolic and 60 diastolic; an obese, dull child; skin very dry and scaly. The heart, lungs, abdomen and genitalia were negative. The basal metabolism was minus 10 per cent. In January, 1943 a low calory diet and thyroid therapy was instituted, beginning with ½ gr. desiccated thyroid and Feosol two tablets three times a day.

*Course:* Following this there was progressive improvement. In June 1943 there was a loss of weight of 7 lbs. with an increase in height of 1½ inches. The basal metabolism was plus 13 per cent. The skin was less dry and no longer scaly. The sluggishness and dullness

had disappeared and marked improvement in school work was reported. By September, 1944, the basal metabolism rate was plus 11 per cent and the weight 82½ lbs., the height 56½ inches. The child is now normal in every respect and has daily bowel movements. She had very little difficulty with her pollen allergy. There have been no asthmatic attacks.

*Case 7.* (Courtesy of Dr. R. Sussman.) *History:* J. N. came under observation at the request of his otolaryngologist on May 1, 1943. He had observed puffiness about the eyes for the past two weeks and difficulty in breathing through his nose and believed that he was suffering from some kind of allergy. In addition he felt tired and sluggish and cold weather distressed him. His family history is significant in that one brother had a coronary thrombosis at the age of 23 and a second brother had a similar attack at the age of 49. One other brother has leukemia. The father died of coronary thrombosis. He had scarlet fever at the age of 5 which was followed by an acute nephritis. Since his discharge from the army about a month ago he has had slight dyspnea on moderate exertion and felt extremely sluggish.

*Examination:* The patient weighed 178 lbs.; his color was pasty, his eyelids puffy. The mucous membranes of the nose were pale and succulent and there was an obstruction to inspiration on both sides. The heart rate was 80 per minute, and regular. The blood pressure was 110 systolic and 90 diastolic. The first sound at the cardiac apex was reduplicated; A2 was louder than P2. The electrocardiogram at this time revealed evidence suggestive of myocardial damage; an iso-electric T-1, low T-2 and inverted T-4. A tentative diagnosis of myxedema with myocardial damage and allergic effects was made. A basal metabolism done in May 1943 was minus 42 per cent. The urine examination at this time was negative; specific gravity, 1.033. A recheck of the basal metabolism was minus 35 per cent. The patient was placed on thyroid (Armour) in doses of 1 grain a day and was frequently observed. Within two weeks his weight was 170 lbs. Blood pressure, 120 systolic and 80 diastolic, and the electrocardiogram revealed definite changes toward the normal. The patient reported feeling very much better; the nasal mucosa had shrunk to normal and there was no more difficulty with inspiration. The puffiness about the eyelids had disappeared. Fluoroscopic examination of the heart showed that the cardiac contour had decreased in size. One month later the basal metabolism was minus 12 per cent. He is now taking 1 grain of thyroid daily. His current weight is 168 lbs. and he is feeling well. His hemoglobin is 100 per cent; the blood cholesterol is 145 mgs. per 100 cc.

Our concepts of disease are often so categorical that only the gross and most obvious evidence is regarded as conclusive. Laboratory findings are often relied on to decide a clinical question. No clinician will deny the value and the aid often derived from the laboratory but it is well to remember that biological processes often interact in such a way as to neutralize the evidence by which one single disturbance might reveal itself. Thus, the significance of negative laboratory findings is not always realized or appreciated. The presence of normal or nearly normal values in disease may represent a readjustment and a balanced effect of a number of biologic processes.

These observations gain especial significance in the consideration of the relation of the thyroid to allergic conditions. Certain criteria have been established for the evaluation of thyroid function, chief of these are the basal metabolism and the lipid content of the blood. In Graves' disease the basal metabolic rate rises, while the cholesterol content of the blood falls. Conversely, in myxedema the basal metabolic rate falls, and the cholesterol content of the blood rises. But we all know that there are a great many intermediary stages

between these two extremes in which these criteria fail to correspond with the clinical evidence, and many bizarre combinations occur. Thus contrary to the established rules, an elevated basal metabolic rate may be accompanied by an increase in the cholesterol content of the blood and vice versa. These contradictory findings assume significance when one takes cognizance of the fact that they are the result of biologic readjustments.

Allergy has been defined as a state of altered reactivity of the tissues to various stimuli conditioned by the antecedent sensitization by the same or allied stimuli. In a previous publication on "The Reciprocal Functions of the Thyroid Gland and Iodine" I pointed out the relation of the thyroid and of iodine to tissue reactivity in general. Whether the effect upon the tissues is a direct, or an indirect one, through the autonomic nervous system, or through the remote action upon the adrenals, is not certain. Whereas thyroid extract heightens tissue reactivity, iodine lowers the reactivity of tissues to sensitization by proteins, and histamine or the H-substance, which is believed to be operative in the production of allergic conditions. We know that while some people, through hereditary influences or by acquired sensitiveness become peculiarly reactive to various stimuli, others do not. From these observations one gains the impression that beneath the increased sensitivity, this inherited or acquired tendency, there is another substrate of altered tissue reactivity which is the result of thyroid dysfunction or iodine deficiency.

The therapeutic implications of this hypothesis are quite obvious. It is true, that when two distinct causes can work synergically in the production of one disease, we can conceive that the removal of either may result in a return to the normal balanced state. In applying this thought to allergy, we find that this dictum is true only in part.

The allergic individual is like the person who stands on the edge of a precipice. Many influences may cause him to fall. A dizzy spell, a gust of wind, a loose rock; all, or any of these may be the cause of his undoing. To ward off dizziness, to erect a shelter from the wind, or to reinforce the ground may protect him from a fall, but in the end he still remains on the edge of a precipice and always in potential danger. The measures employed in the treatment of allergic diseases are of this order—they may relieve, but they do not eliminate the fundamental susceptibility. Removing the offending allergens, desensitization or change of climate or locality are only palliative measures, which do not obviate the fundamental cause of the disease. To this end proper inquiry into the behavior of the thyroid gland by laboratory study and therapeutic test should be made in all cases of allergy, certainly in those cases which prove refractory even to palliative treatment. I have no desire to create the impression that the modern methods of allergic treatment are not well-founded or that they are ineffectual. I do feel, however, that they do not strike at the core of the trouble, and for that reason, the results attained often lack permanency. Associated etiologic factors must be sought for and eradicated or corrected in order to effect a fundamental and lasting cure.

## SUMMARY

From the observations made I would venture the following conclusions:—

1) When hereditary factors play a part in allergic conditions other hereditary stigmata may also be found, and those pointing to thyroid dysfunction are not uncommon.

2) Hyper-reactivity of tissues due to thyroid disturbances often precedes and forms the substrate for allergic sensitization.

3) The presence of thyroid dysfunction may not be demonstrable, when the allergic condition is in evidence. Only in later years the thyroid factor may become predominant.

4) It is necessary to direct attention to the thyroid factor in the treatment of allergic diseases.



# AN EVALUATION OF THE KENNY TREATMENT OF POLIOMYELITIS

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The Kenny Method was started by an Australian nurse who learned nursing in a small, private, rural hospital. She did her early work in the Australian Bush Country. There she saw paralyzed patients and in attending them became interested in physical therapy and muscle training. After having evolved her own technique, she applied certain medical terms to these manipulations. Australian physicians who learned of her work became interested in it, but because of her lack of medical knowledge, were reluctant to accept her new terminology and technique in the treatment of patients with poliomyelitis.

After having travelled to England where she was coldly received, Sister Kenny came to America in 1940 and was granted the privilege of treating patients in Minneapolis, Minn. Following the initial clinical trials, she was sponsored by the National Foundation for Infantile Paralysis. This resulted in enormous publicity, especially in the lay press. Medical clinics all over the country became interested and when poliomyelitis struck, as it did in many parts of the United States during the past four years, the question of applying the Kenny treatment immediately arose (1).

As a result, there have been a number of reports on the Kenny Method, most of them having been written by orthopedists. It is the purpose of this paper to discuss the subject from the point of view of a pediatrician who has observed the use of the Kenny Method during two recent, large epidemics.

Before so doing, I would like to summarize briefly the reactions of the various groups of specialists to the treatment in order to give an over-all picture of the medical profession's attitude to such a revolutionary method.

In the first place, the orthopedists' reaction was mixed, perhaps because of Sister Kenny's lack of medical knowledge of the disease and the fact that advance notices of the method were not favorable. Because of their antagonism the orthopedists at first, and even now in some instances, have failed to evaluate properly the beneficial features of the treatment (2). On the other hand, the pediatricians, for the most part, accepted the method, but with some reservation and what may be termed healthy skepticism (3). The physical therapists immediately favored it since it greatly increased their prestige. Hospital administrators were confronted with the problem of having poliomyelitic patients occupy beds for months because of the reluctance of physical therapists to consider cases well enough after a few weeks to be discharged from hospital beds and be treated ambulatorily. The nursing staffs were at first violently opposed to the method because it required so much nursing time, however, they soon learned that nurses readily could be trained in the new technique. With the aid of the National Foundation, ringers, blankets and rubber sheeting, etc. were procured, and nurses soon were proficient in the proper application of these materials.

Before going further in the discussion, let us first remember that poliomyelitis is a disease which varies greatly in severity and in which some patients, apparently badly paralyzed, may make an excellent functional recovery. Sherman (4), in a recent study, showed again that the spontaneous course is usually favorable. On the other hand, some patients with less involvement do not necessarily recover completely.

Furthermore, in evaluating any therapy in poliomyelitis one must remember that in all epidemics there are large numbers of non-paralytic cases. For example, in the last large New York City outbreak in 1931, perhaps 60 percent of all patients reported did not become paralyzed or at least so slightly paralyzed that their muscle weaknesses were negligible. With increased alertness on the part of physicians when the incidence of poliomyelitis rises, more mild cases are diagnosed. The existence of large numbers of non-paralytic cases reminds one very much of the issue raised by some of us in 1931 over the routine use of convalescent serum. It was held by many that convalescent serum neutralized the virus and that many cases of paralysis were prevented or arrested by its use. It was subsequently shown (5), however, that the spontaneous course of the disease often ended before paralysis occurred and physicians soon realized that they no longer need use serum. They also saw that serum did not prevent death in the fulminating bulbar cases. We now find ourselves again in a similar situation with a new and more difficult therapy to evaluate.

Let us enumerate the advantages of the Kenny Method:

First, in the early stages of the disease the application of hot packs to painful areas has definitely lessened pain and improved the general well-being and comfort of the patient.

Second, the so-called spasm in the muscles which are painful seems to disappear more quickly following the use of the hot pack than was formerly the case.

Third, technicians have trained the patient in the knowledge of how to use the muscles of the body. This has been called "awareness" and has been distinctly helpful in retraining.

Fourth, the application of fixed casts to patients in the early part of their disease has been eliminated. Most authorities agree that this was harmful in many cases. Without fixed casts some disuse atrophy has been prevented and some muscles have been given the benefit of earlier massage with a resultant improvement in their tone.

Fifth, even in cases in which there is extensive paralysis, muscles have been kept from contracting and other muscles have been trained to substitute for the paralyzed ones. This requires continued concentration and control, and months and even years of training. Nevertheless, if a good result is achieved, the time, money and energy spent have been worthwhile. Orthopedists, however, feel that contractures result even after a year of Kenny treatment as soon as muscles are put to work, just as was the case in past years after paralyzed muscles were removed from plaster of Paris bandages.

Sixth, the method has increased the care which patients receive in the early

stage of their disease. Formerly nursing and medical care, especially in contagious disease hospitals, was necessarily perfunctory because of the case load which existed during epidemics. Now trained technicians are supplied, and patients are more frequently examined for muscle weakness.

Now as to the disadvantages:

First, under its present set-up, much of the treatment has been taken out of the hands of physicians and has been taken over by physical therapists, or merely by so-called Kenny technicians. It is obvious that any disease with as many different and threatening manifestations as poliomyelitis needs thorough medical supervision. In this connection, Sister Kenny's objection to the use of the respirator in cases with intercostal muscle involvement requires no comment.

Second, the failure of physical therapists to invite orthopedists and accept their advice and recommendations for splinting is deplorable. Even the use of movable casts, a compromise with the older fixed orthodox cast, has been frowned upon by the Kenny advocates.

Third, many of the ritual features are superfluous and perhaps harmful. For example, the giving of an enema at the start of treatment to a child who may have a parietic bowel or bladder is certainly contraindicated. A minor objection, but of considerable psychological importance, is the taking away of a child's pyjamas. In one instance this created such a feeling of insecurity that the child fell asleep from sheer exhaustion after an hour's tantrum. The roughness of the wool blankets, which are used instead of bed sheets cause annoyance to some patients. There seems to be no valid reason why sheeting cannot be employed during the greater part of the day and night. The use of footboards is utterly without reason in patients who have no evidence of leg or thigh weakness. Moreover, most patients roll or roam about the bed at will and the footboards are useless to them anyway.

Fourth, another unfortunate factor is the use of new medical terminology which includes phrases like "mental alienation" which has a questionable meaning.

Fifth, frequent packing sometimes produces fatigue which in cases of extensive muscle involvement is of no therapeutic advantage.

Sixth, instances of scoliosis have been observed within three months of the onset in cases pronounced non-paralytic and free of spasm after receiving Kenny treatment. This disproves one statement that has been made, namely that poor end results in the past were due to missed muscle spasm or paralysis which would have been picked up with the Kenny technique.

Seventh, most unfortunate has been the inclusion in statistics of cases that have not been treated adequately by the Kenny Method. The case loads in some hospitals are often so great that patients are packed only once or twice a day, yet these patients are considered as having received the Kenny treatment when their case is reviewed. Furthermore, as soon as children feel better they will not lie prone. On the contrary, they jump up and down or may get out of bed and run about the ward. Can these cases also be included in those who have recovered with the help of the Kenny treatment?

Eighth, the method is expensive, laborious, time-consuming and requires prolonged hospitalization. If it is proven superior, all this is justified. At present, however, this is a moot question.

There have been some attempts to compromise the advantages and disadvantages of the method. Unfortunately there has been a good deal of acrimonious debate for and against the method with the result that even the many published reports still leave us in doubt (6). In the non-paralytic cases there surely can be little or no difference whether a patient is treated with hot packs or not as far as his end results are concerned. It is granted, however, that there is some measure of increased comfort from the packs. Since we have said that perhaps 60 percent of all cases in most modern epidemics are non-paralytic, it becomes a question as to whether an expensive and time-consuming method shall be instituted at the start in every case admitted to a hospital with a diagnosis of poliomyelitis. Sister Kenny considers that the skin, subcutaneous tissue, fascia, muscles and tendons are involved in all cases. She believes it is important to apply hot packs to all muscles and tissues which are in spasm. This is a theory which is open to question, for as every physician who has had any knowledge of poliomyelitis knows, neck spasm or rigidity, for example, is the result of meningeal irritation. As soon as the inflammation of the meninges subsides so does the neck rigidity. Sister Kenny explains it differently. She considers this spasm a symptom of muscle pathology. But the evidence of primary myopathy in poliomyelitis is unproven. While there are occasional cases in which neck muscle weakness follows the early rigidity, this is not as common as the usual reflex spasm from meningeal inflammation. There is no objection to applying hot packs to the neck in every case showing neck rigidity, but it would only seem to be indicated in those cases in which there is a good deal of pain. Similarly, hamstring spasm is present in every case. We have always considered it a sign of lower lumbar meningeal irritation and have called it Kernig's sign. The physical therapists call it spasm of the hamstring muscles and tendons and believe that each case showing it should be packed. Hamstring spasm also disappears in the average case within from one to ten days. If we should pack all patients with a positive Kernig sign, should we not pack patients who have this sign as a result of other spinal cord inflammation such as meningococcus infections? Obviously, this is unnecessary. Then—shall we pack the rest of the body in cases showing only neck or hamstring spasm? I think the answer lies in whether or not there is pain or tenderness in any portion of the skeletal structure. Muscle pain then, is the chief symptom which requires the use of Kenny packs. Patients receiving the pack certainly seem to be more comfortable than they were in previous years when they received treatment with casts or no treatment at all.

So much for the mildly paralyzed or non-paralytic patient. The question as to how to treat patients with extensive muscle involvement is not as easy to answer. After the acute stage of the disease, most of the improvement takes place within the first eighteen months. Most orthopedists who have seen a good many cases treated by the Kenny Method, feel that the end results are not

much different than they were in former years. Moreover, the new treatment cannot, nor does it in fact claim to restore muscle functions in such muscles as were formerly classified as "trace" or "gone" in respect to power. Whether hot packs help such cases is very questionable. Patients seem to develop spasm or retain their spasm as soon as they begin to use their muscles, regardless of the claim of physical therapists to the contrary. Moreover, one sees the technicians stretching the muscles just as the orthopedists did in former days. However, if such patients, because of a spotty type of paralysis, have fortunately retained the use of closely associated muscle groups, then re-education therapy may be extremely helpful in restoring function. Kenny-trained physical therapists do this very well. Of course, many orthopedic hospitals instituted re-education therapy in the past, but it was not as well planned or as widespread as it is now. How much the muscles have been "upgraded" is again a matter of subjective evaluation. Sometimes the improvement is striking, at other times disappointing with the Kenny technique just as it was following removal of casts in former years. We must not forget that we cannot hope for return of muscle function in patients whose anterior horn cells have been largely destroyed. The chief pathology, in spite of Sister Kenny, is in the spinal cord and brain.

I have enumerated the advantages and disadvantages with a brief discussion of the results of the new method. Whether we are actually seeing better end results has not been answered and will not be answered until a team of unbiased physicians treats every case of poliomyelitis from its onset.

The final responsibility for the care of these patients should be in the hands of a physician who has been trained in the treatment of infectious diseases. He should be willing and eager to call on the neurologist, the orthopedist and the physical therapist for assistance as soon as the indications for their help arise. For any one of these specialists alone cannot hope to give the patient his best possible chance for complete recovery.

Perhaps some sort of registry could be set up so that all cases of poliomyelitis throughout the country could be tabulated according to muscle involvement. Patients could be examined and graded in a standard way every three or four days at the onset and, after a while, every week or two. In such a way progress according to one or another method of treatment could be definitely evaluated.

In conclusion we must acknowledge our debt to Sister Kenny for her demonstration of what she calls "muscle spasm." Most of us will agree that in former years we either overlooked this symptom or paid little attention to it. Despite the controversial aspects of her method, Sister Kenny has stimulated our thoughts, she has made us educate more people in the technique of muscle training and has led us to think along new lines in the investigation of the treatment of poliomyelitis.

#### BIBLIOGRAPHY

1. COLE, W. H., POHL, J. F., AND KNAPP, M. E.: *The Kenny Method of Treatment for Infantile Paralysis*. New York, The National Foundation for Infantile Paralysis, Publication No. 40.



2. KEY, J. A.: Kenny versus Orthodox Treatment of Anterior Poliomyelitis. *Surgery*, 14: 20, 1943.  
McCARROLL, H. R., AND CREGO, C. H., JR.: An Evaluation of Physiotherapy in the Early Treatment of Anterior Poliomyelitis. *J. Bone & Joint Surg.*, 23: 851, 1941.  
GILL, A. B.: The Kenny Concepts and Treatment of Infantile Paralysis. *J. Bone & Joint Surg.*, 26: 87, 1944.
3. DALY, M. M. I., GREENBAUM, J., REILLY, E. T., WEISS, A. M., AND STIMSON, P. M.: Early Treatment of Poliomyelitis with Evaluation of Sister Kenny Treatment. *J. A. M. A.*, 118: 1433, 1942.
4. SHERMAN, M. S.: The Natural Course of Poliomyelitis. *J. A. M. A.*, 125: 99, 1944.
5. FISCHER, A. E.: Human Convalescent Serum in the Treatment of Preparalytic Poliomyelitis. A Comparison of 477 Treated and 102 Control Patients in New York City in 1931. *Am. J. Dis. Child.*, 48: 481, 1934.
6. RANSOHOFF, N. S.: Experiences with the Kenny Treatment for Acute Poliomyelitis in the Epidemic of 1942, Monmouth and Ocean Counties, New Jersey. *J. Bone & Joint Surg.*, 26: 99, 1944.

## COMPRESSION FRACTURE OF THE SPINE IN THE CAROTID SINUS SYNDROME<sup>1</sup>

ARTHUR M. FISHBERG, M.D., AND ROBERT K. LIPPMANN, M.D.

It has long been known that the convulsions of epilepsy and the spasms of tetanus may, through muscular action, cause fractures of the spine. Greater interest in this form of spinal compression fracture was aroused when Stalker (1) and Wespi (2) independently described the occurrence of such fracture as a result of the convulsions induced by the metrazol treatment of psychosis. Further observations have shown that compression fractures of the vertebrae complicate metrazol convulsive therapy frequently enough to form a serious drawback. Polatin and his associates (3) found compression fractures of the spine in the roentgenograms of 43.1 per cent of patients in whom they had induced convulsions by metrazol. Barrett, Funkhauser and Barker (4) observed the remarkably high incidence of 45 per cent of compression fractures in epileptics. The fractures also occur, although much more rarely, after electric shock treatment. Spinal fractures resulting from metrazol convulsions almost always involve the dorsal vertebrae and are usually multiple. They are compression fractures due to acute anterior flexion of the spine. Since only the vertebral bodies are involved and there are no dislocations, it is not surprising that neurological signs or symptoms due to injury to the cord or roots are rarely, if ever, seen. Except apparently in tetanus, with which we have no personal experience, healing seemingly always occurs with little or no deformity.

In this paper we desire to describe the occurrence in carotid sinus convulsions of compression fracture of the spine identical with that hitherto observed in the convulsions of shock treatment, epilepsy and tetanus. So far as we are aware, compression fracture of the spine has not hitherto been described as a complication of the carotid sinus syndrome.

### CASE REPORT

*History:* A manufacturer of fifty-five years was first seen by one of us (A. F.) on March 28, 1938. He complained of syncope which had recurred since childhood. The syncopal attacks came on suddenly and lasted but a few seconds. He lost consciousness completely during the attack. He had injured himself as a result of a fall in an attack. He felt completely well soon after regaining consciousness after an attack. The attacks had been increasing in frequency in recent years. The patient knew of no factors which tended to precipitate an attack.

Examination of the patient revealed that he was suffering from the carotid sinus syndrome. Relatively light massage of the right carotid sinus produced complete cardiac standstill which was followed in ten or fifteen seconds by complete loss of consciousness, and then by tonic and clonic convulsions of extreme severity. The development of the convulsions was so dramatic that more accurate observations could not be carried out: all the efforts of the nurse present and one of us had to be devoted to preventing the patient from falling off the table as a result of his convulsion.

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<sup>1</sup>From The First Medical Service of Dr. George Bachr and The Orthopedic Service of The Mount Sinai Hospital, submitted for publication November 5, 1944.

The patient was so terrified by what had happened that he has since refused again to permit the reproduction of the attack by pressure on the carotid sinus.

The patient was instructed to wear a loose collar and given atropine. The attacks became much less frequent. In January, 1942, the patient went to Florida. There he felt so well that he discontinued the atropine of his own volition. He returned to New York, February 12. That day he was seated in a chair and was speaking and gesticulating emphatically to several members of his family when they observed that he had lost consciousness and was in an intense clonic convulsion. He began to slump out of the chair toward the floor when they rushed to his aid and laid him on the floor. The excitement was such that the witnesses could not describe accurately the duration of either the syncope or the convulsion. All were agreed, however, that the patient had sustained no fall or blow that could have produced direct or jack-knifing impact to the spine proper. When he regained consciousness, he complained of intense pain in the middle of the back. Morphine was required to control the excruciating pain.

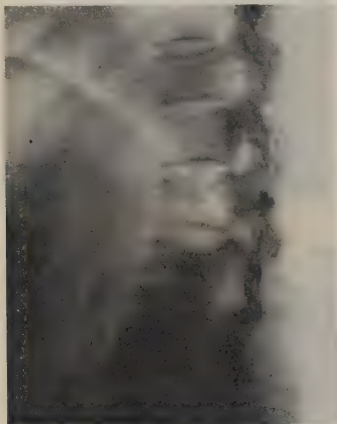


FIG. 1

Examination at this time revealed a tender gibbus corresponding to the dorso-lumbar spine. Percussion over this area caused severe pain and the spine was maintained inflexible by severe muscle spasm. The neurological status was negative. The history and findings suggested spine fracture secondary to the muscle pull of the convulsion.

The patient was immediately referred to The Mount Sinai Hospital where x-rays disclosed a partial compression fracture of the body of the twelfth dorsal vertebra with collapse of about three-fourth of normal vertebral height as well as compression of the first lumbar vertebral body to one-quarter normal height (fig. 1). Without anesthesia, correction of the deformity was attained by the use of "Goldthwaite irons" and the spine immobilized in a hyperextension jacket. Check-up x-rays taken through the jacket showed excellent correction of compression (fig. 2).

In the hospital, the patient was kept in bed on a board while physiotherapy was applied to his extremities. There were no complications. He commenced sitting and standing one month later. Walking was allowed six weeks after the injury and was not accompanied by pain.

Three months after the injury, the plaster jacket was removed and a brace applied which was discarded gradually over a period of eight weeks. Check-up x-rays at intervals



FIG. 2



FIG. 3

revealed satisfactory maintenance of position and complaints were minimal. Mobilization exercises were instituted four months after the injury and two months later, or six

months after injury, there were no remaining subjective or objective clinical evidences of the back trauma.

The last x-rays taken on July 27, 1942, seventeen months after injury, revealed complete restitution of the twelfth dorsal vertebra and restitution of the first lumbar vertebra to approximately four-fifths of its normal height (fig. 3).

#### DISCUSSION

The above observation adds hypersensitive carotid sinus to shock treatment, epilepsy and tetanus as a cause of convulsions which may produce compression fractures of the spine. Doubtless, the carotid sinus syndrome is a rare cause of such compression fractures because it only exceptionally produces sufficiently violent convulsions. Treatment of the condition differs in no important respect from that of other spine fractures, except for the need of avoiding any risk of pressure over the vicinity of the carotid sinus by the immobilizing apparatus.

#### REFERENCES

1. STALKER: *Lancet*, 2: 1172, 1938.
2. WESPI: *Schweiz. Arch. Neurol. u. Psychiat.* 42: 404, 1938.
3. POLATIN, FRIEDMAN, HARRIS AND HOROWITZ: *J. A. M. A.* 112: 1684, 1939.
4. BARRETT, FUNKHAUSER AND BARKER: *Am. J. Psychiat.* 99: 387, 1942-43.



## ULCERATIVE COLITIS: A COOPERATIVE HOSPITAL PROBLEM

JOHN H. GARLOCK, M.D.

It is because of Dr. Moschcowitz's great interest in psychosomatic medicine that I bring up for rediscussion the problem of ulcerative colitis. It is one of the few examples of psychosomatic disease that requires the combined efforts of so many members of the hospital staff, and it is this feature of the management of ulcerative colitis that I would like to emphasize at this time.

The sequence of events in the development of ulcerative colitis from its onset to the later stages of hyperplasia and polypoid degeneration and even carcinomatous transformation gives one food for considerable speculation. That the disease in its initial phases has a strong psychogenic or neurogenic background there can be little doubt. I might mention briefly the provocative experiments of Penner and Bernheim and the reports from England of the effect of the aerial bombardment of London in 1940 on the intestinal tracts of dogs. Once ulcerations of the mucosa develop, whatever their primary cause may be, secondary infection from the intestinal tract becomes a prominent part of the picture and the disease progresses to infiltration of the colonic wall by the products of inflammation, the formation of scar tissue and polypoid degeneration of the mucosa. There are exacerbations and remissions with gradual progression of the pathologic process until the colon is converted into a greatly thickened, fibrotic, shortened tube, lined by infected granulation tissue exuding pus and blood. The progress of the disease in the colon is reflected in the patient's general condition. Because of frequent rectal discharges with associated loss of fluids and the general toxemia caused by absorption from the diseased bowel, gradual physical deterioration takes place with weight loss, anemia, avitaminosis and toxic manifestations, such as fever, arthritis, skin infections and ulcerations, etc. With the underlying psychogenic basis for the disease still operative, perhaps considerably magnified because of the now important physical aspects of the disease, the patient presents one of the most pitiable pictures in the whole field of medicine.

The management of ulcerative colitis as we see it at The Mount Sinai Hospital is a cooperative problem and involves the services of physician, gastro-enterologist, radiologist, proctologist, psychiatrist, the nursing staff, surgeons interested in and conversant with the various aspects of the disease, hematologist, dermatologist and the social service worker. In order that the treatment of the disease may be most effective, it is important that each patient be individualized and that his problem be appraised by the whole group. In the treatment of this serious ailment there is no room for hide bound convictions and methods of therapy that have passed their period of usefulness. There must be elasticity of thought in its application to the problem at hand. Only in this way can we develop methods of therapy which will produce increasingly more favorable results.

On the wards of the hospital, we see the disease in various stages of its develop-

ment. In approximately 80 per cent of the patients, it can be effectively controlled by the combined efforts of the medical staff, gastro-enterologist and psychiatrist. However, in the remaining 20 per cent, conservative medical treatment fails and more radical management must be considered. Although the surgeon should be one of the team managing the cases in the 80 per cent group, he becomes an important factor in the treatment of the 20 per cent group because it is in this group that surgical therapy becomes indicated. Since 1937, when the group treatment of this disease was undertaken, it has been our objective to establish criteria, acceptable to all, for the surgical treatment of ulcerative colitis. Perhaps because of the war, in spite of the fact that the stress and strain of the war has probably increased the incidence of the disease, it has seemed that these criteria are not as clearly appreciated as heretofore. The time seems opportune, therefore, to restate our views on the surgical management of ulcerative colitis as part of the general therapeutic picture.

In the past, the surgical treatment of this disease consisted of appendicostomy, cecostomy and loop ileostomy. The latter usually accomplished its purpose of diverting the fecal stream but was usually followed by marked prolapse of the ileum. The purpose of the other procedures was primarily to permit of irrigation of the diseased bowel with medicated solutions. Experience has shown that this form of therapy was based on fallacious reasoning and that the important requisite of successful surgical treatment was complete diversion of the fecal stream. On the basis of our experience to date, it is generally agreed that surgery is indicated in the treatment of ulcerative colitis under the following conditions:

1. Uncontrollable bowel hemorrhage
2. Acute ulcerative colitis with profound toxemia not responding quickly to conservative means
3. Impending perforation of the colon
4. Chronic intractable colitis with extensive scarring, polypoid degeneration or recto-vaginal fistulae
5. Segmental colitis.

Furthermore, it is our conviction that ileostomy is indicated as the initial surgical procedure under the following circumstances:

1. For uncontrollable hemorrhage. Complete diversion of the fecal stream puts the diseased bowel at rest and minimizes the likelihood of further bleeding.
2. For acute colitis with profound toxemia. The course of the disease is short and fulminating and the patients are desperately ill. Without operation, the mortality is very high. Our experience indicates that the *early* performance of ileostomy is a life-saving measure. It is particularly in this group that medical treatment should not be prolonged and that the surgeon should be called early in the course of the disease. There are too many instances of fatal procrastination to warrant continuation of the policy of watchful waiting.
3. For impending perforation. Ileostomy should be performed as an emergency measure.

4. Intractable colitis of the universal variety. Ileostomy is the first step of a graded resection of the colon.

The marked improvement in the general condition of the patient following ileostomy is one of the remarkable features of the surgical treatment of colitis. The weight gain may be up to fifty pounds; the anemia disappears; the appetite improves and the various toxic manifestations abate. In the acute fulminating variety, ileostomy is followed by a dramatic change in the patient with a drop in temperature, often by crisis and a rapid decrease in the rectal discharges. Ileostomy should, in no sense, be considered a curative operation. It is the first stage of a graded operation consisting of subtotal or total colectomy. It is important to emphasize that we have observed active disease still present in the colon two years after its exclusion by ileostomy. Therefore, re-establishment of continuity of the ileum is fraught with great danger.

If the disease is confined to the left colon and rectum and operation is deemed advisable, transverse colostomy instead of ileostomy may be carried out. This is followed at a later date by resection of the left colon and rectum, also, if indicated. If the rectum and lower sigmoid are found, on sigmoidoscopic examination, to be free of disease, the initial operation of choice is an ileosigmoidostomy or ileoproctostomy with division of the terminal ileum and transection of the colon proximal to the anastomosis. At a later date, the excluded diseased bowel is removed. The follow-up results in this group have been excellent.

When ileostomy has been performed as the first stage of a graded procedure, the nature of the subsequent steps will depend upon a number of factors. If the disease is universal and there is hopeless involvement of the rectum as well, as indicated by the presence of polyposis, strictures or recto-vaginal fistulae, further surgery will consist of first, a subtotal colectomy and second, an abdominoperineal resection of the rectum. If, however, the rectum is not too severely involved, it is our policy to do a subtotal colectomy and preserve the lower sigmoid and rectum for possible future use in re-establishing intestinal continuity. In seven patients, after a wait of two to three years and repeated examinations indicated apparent complete cessation of the disease and return of the mucosa to normal, we disconnected the ileostomy and re-established intestinal continuity by uniting the ileum and upper rectum. The results have been astonishingly good. It, therefore, should become apparent to the physician that ileostomy should no longer necessarily be considered a permanent disability for the patient. With a modern viewpoint, based on rapid progress in surgical technique, an appreciable proportion of these patients may be restored to normal physiological intestinal function.

The thoughts expressed in this paper are based on an analysis of 68 patients treated surgically between September 1937 and April 1944. The results of this inquiry will be published shortly. Suffice it to say now that the mortality of ileostomy has been reduced from the old figure of 70 per cent to 15.7 per cent. The mortality of colectomy has proportionately been decreased. In the group of 13 primary ileosigmoidostomy or ileoproctostomy followed by colectomy, there

was only one instance of progression of the disease to the rectum. The results in the group of segmental colitis have been unusually good. All survivors have been transformed from chronic invalids to healthy useful members of society.

I would like to stress again that this marked improvement in the results of surgical therapy over those in by-gone years has been made possible by the concerted efforts of all the workers enumerated in the beginning of this paper. It serves to emphasize the necessity of considering ulcerative colitis as a group hospital problem.

## SIGNIFICANCE OF GASTRIC-JUICE DEPLETION ON THE EFFECT OF NOVASUROL DIURESIS

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Despite numerous investigations regarding the effect of Novasurol on blood and tissue chlorides, the question still remains as to the extent to which the chloride level of the body is concerned in the diuretic action of this compound as well as of organic mercurial salts in general. Ethridge, Myers and Fulton (1) have attempted to demonstrate by experimental diuretic tests on dogs that the simultaneous administration of two neutral salts, such as sodium chloride or potassium chloride with Salyrgan, resulted in no appreciable change in the diuretic response such as is noted following the administration of Salyrgan alone. Fliederbaum and Krasucka (2), moreover, observed a lowered response to Merbaphen after the ingestion of sodium chloride.

On the other hand, clinical experiences have demonstrated that in cases of hypochloremia where ordinarily organic mercurial diuretics are ineffective, the addition of sodium chloride can result in prompt mercurial diuresis [Goldring (3)]. According to Melville and Stehle (4), the principal effect of Novasurol is based on the presence of sodium chlorides and the diuresis of salts is accomplished by means of the excretion of sodium chloride from the tissues.

The importance of the tissue chlorides in mercurial diuresis is illustrated by the fact that in a patient kept on a diet rich in sodium, but lacking in chlorides, the previously satisfactory mercurial diuresis disappears as a result of the relative chloride deficiency in the presence of an excess of sodium in the tissues [Schoenholzer (5)].

Moreover, the significance of availability of the chlorides for the production of mercurial diuresis can be illustrated by the disappearance of the diuretic effects of Salyrgan on dogs rendered hypochloremic by a biliary fistula [Claussen (6); Evans (7)] and the reappearance of the diuretic response following the administration of sodium chloride.

Clinical experience has pointed to another important factor besides the chlorides. Keith and Whelan (8), Saxl and Edlbacher (9), Engel and Epstein (10) made it clear that an acidifying salt such as ammonium chloride increases Novasurol diuresis by producing acidosis as shown by a fall in the alkali reserve and an increase in the hydrogen concentration of the blood plasma, while an alkalinizing substance such as sodium bicarbonate reduces and inhibits mercurial diuresis, shifting the acid-base balance of the body fluids in the opposite direction.

This brief review of the literature reveals that the diuretic action of organic mercurial salts not only depends upon the *state of hydration*, which is equally important for all diuretics but principally upon two other factors: 1. *a sufficient chloride-level* in the blood and tissues, 2. *a certain degree of acidification* of the



body. Should these conditions not prevail, organic mercurial diuretics remain ineffective.

To test the validity of the aforementioned view, investigations were carried out on five dogs with a stomach fistula in which the latter could be kept closed or opened during an experiment. It is, therefore, possible in a dog with an open fistula to produce conditions which are encountered in certain diseases as in pylorospasm with its prolonged emesis leading to hypochloremia, alkalosis and dehydration. Dragstedt (11) and Ivy (12) and their co-workers have already demonstrated in animals that the removal of the gastric juice by means of a fistula results in a 50 per cent reduction of the blood chlorides, alkalosis, marked dehydration and in a rise in the non-protein nitrogen of the blood.

#### METHODS

Our experiments were carried out on female dogs weighing 15 to 20 Kg. *Bladder-fistulas* were created according to the usual technique. Three weeks

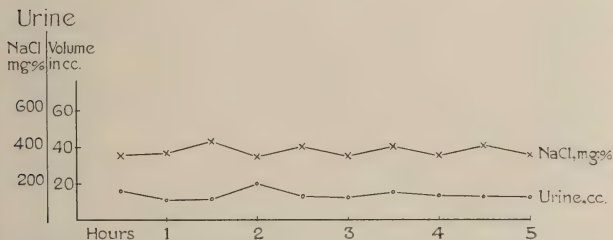


FIG. 1. Urine and NaCl excretion without treatment; stomach fistula closed.

after the animals had completely recovered from the operation, *gastric fistulas* were established (13). The animals were subjected to the experiments only once a week. The animals were fasted 14 hours previous to the experiment and no water was given to the dogs during the test period. Spontaneous urine output was recorded in the case of each dog with closed and opened gastric fistula. The dogs were kept in harness during the experiment. The urine and the gastric juice were collected at half-hour intervals, the volume of the samples were measured and the quantity of sodium chloride was determined in both urine and gastric juice specimens. Novasurol was used in doses of 5 mg. per Kg. and injected subcutaneously. The duration of the experiment was usually five hours.

#### RESULTS

The results obtained were similar in all the animals used; the typical findings on one of the dogs are represented in figures 1 to 5.

Figure 1 shows the spontaneous urine output and its sodium chloride concen-

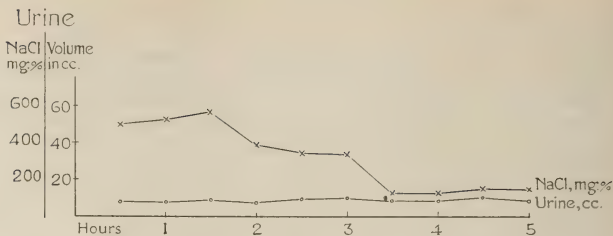


FIG. 2. Urine and NaCl excretion without treatment; stomach fistula opened.

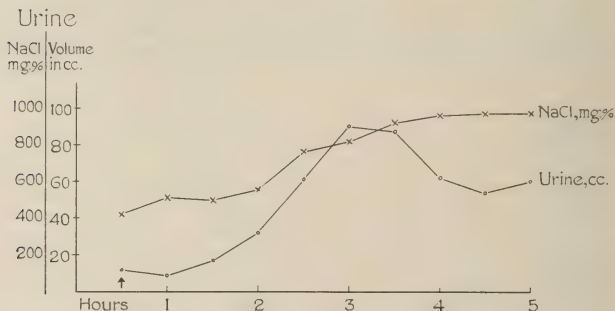


FIG. 3. Urine and NaCl excretion after injection of Novasurol at ↑; stomach fistula closed

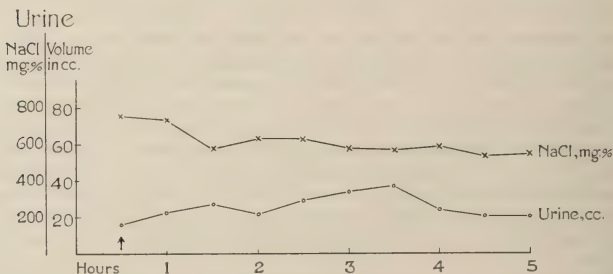


FIG. 4. Urine and NaCl excretion after injection of Novasurol at ↑; stomach fistula opened.

tration. The gastric fistula was kept closed throughout the experiment. The urine volume and the sodium chloride content of the half-hour specimens remain fairly constant during the 5 hour test period.

Figure 2 illustrates the spontaneous urine output and its sodium chloride concentration when the gastric fistula was kept open. While the urine output remains constant, changes in the sodium chloride concentration can be observed: one and one-half hours after the start of the experiment the sodium chloride concentration begins to decrease and at the end of the test, only one-fifth of the original concentration can be found. During this period, the gastric secretion amounted to 349 cc. containing chlorine equivalent to 2.9 Gm. of sodium chloride.

Figure 3, the animal received *Novasurol* *subcutaneously* at the beginning of the experiment; the gastric fistula was kept closed. The *Novasurol* effect becomes apparent at the end of one and one-half hours after the injection and the urine output begins to increase from 7 to 12 cc. obtained at the start; it reaches a maximum of 86 cc. at the end of the third hour and at the end of the

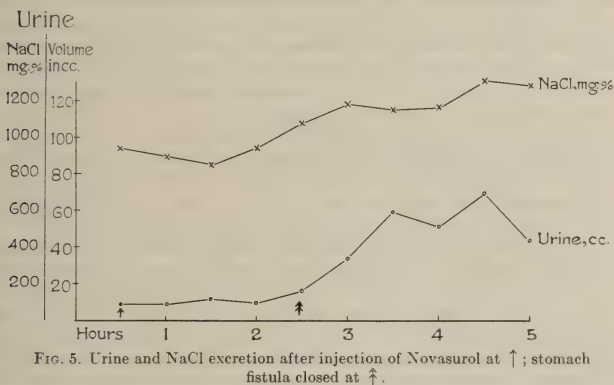


FIG. 5. Urine and NaCl excretion after injection of *Novasurol* at ↑; stomach fistula closed at ↑.

fifth hour the excretion is still 50 cc. During the entire five hour test period, 457 cc. of urine were excreted with the total amount of sodium chloride of 3.6 Gm.

Figure 4 shows the effect of *Novasurol* on the dog in which the gastric fistula was kept open throughout the experiment. In contrast to experiment 3 (fig. 3) with the closed gastric fistula, there was a comparatively slight increase of diuresis and furthermore was an increase of the sodium chloride concentration lacking. The total urine excretion during the entire five hours was 212 cc. and the excretion of sodium chloride amounted to 1.6 Gm. During this period 116 cc. of gastric juice were collected containing chlorine equivalent to 1 Gm. of sodium chloride.

Figure 5, shows the results of an experiment in which *Novasurol* was injected as usual at the start of the experiment, the gastric fistula being kept *open* for the first two hours and then closed for the remaining three hours. Urine and sodium

chloride excretion follow the same pattern as shown in figure 3 where the fistula was kept closed from the beginning of the experiment. This finding shows that the full effect of Novasurol is depending upon the presence of the gastric juice. During a complete five hours experiment, the urinary excretion amounted to 340 cc. with 3.8 Gm. of sodium chloride. During the first test period with open fistula, 97 cc. of gastric juice with chlorine content equivalent to 0.6 Gm. of sodium chloride were secreted with a simultaneous urine excretion of 45 cc.

#### DISCUSSION

The experiments performed on dogs with bladder and stomach fistulas make possible an exact analysis of water and salt excretion under normal conditions, and those following Novasurol administration.

Due to the fact that the gastric juice can be removed at will, means are available to determine its relation to urine and sodium chloride excretion. It was found that the removal of gastric juice in the normal animal hardly affects the spontaneous urine excretion, but influences the sodium chloride concentration of the urine which begins to decrease early in the experiment and after four to five hours amounts to only one-fifth of the original sodium chloride concentration. It seems, therefore, that the normal organism is capable to prevent a serious depletion of the sodium chloride depots by decreasing the output of sodium chloride through the kidneys thus preserving the necessary physiological level of sodium chloride.

The question presented itself as to whether a similar safety-mechanism occurred in the Novasurol diuresis when gastric juice was removed at the same time. This question was of special interest, since Novasurol diuresis is usually accompanied with considerable water and sodium chloride excretion, whereby the excreted amount of salt is not only due to the increased urine output but also the increased urinary sodium chloride concentration. Our experiments studying the effects of Novasurol in dogs with the closed and opened gastric fistulas showed definitely the effect of the loss of gastric juice: the water and salt excretion were distinctly reduced as compared with the values obtained with Novasurol in the dog with the gastric fistula closed. The reduction in the sodium chloride excretion was due not only to the reduced urine output but also to the failure of the kidney to increase the sodium chloride concentration as it is usually observed after Novasurol administration. It may thus be concluded that, in spite of the strong influence of Novasurol on the sodium chloride excretion, the organism still retains the ability to regulate its sodium chloride level and to prevent an excessive loss of sodium chloride by Novasurol.

This competition between the regulation of sodium chloride excretion by the kidneys and the effect of Novasurol on salt excretion is only then apparent when the removal of gastric juice during the five hour experiment is maintained. If, however, the open stomach fistula is closed two hours after the injection of Novasurol, i.e., at the time when the Novasurol diuresis usually begins, then the Novasurol effect is unrestricted and is characterized by both a marked increase in diuresis and in sodium chloride urinary concentration.

It may be, therefore, assumed that the protection of the organism from exces-

sive depletion of the sodium chloride depots is effected by changes in the acid-base balance in the body. The latter appears thus as important regulator in the retention and excretion of the chlorides which play such an important role in the furthering of diuresis in general and the Novasurol diuresis specifically. The necessary blood chloride concentration for optimum diuresis must be reached by a shift of the acid alkali balance toward the acid side.

## SUMMARY

Spontaneous urine excretion and Novasurol diuresis were studied in experiments on dogs with bladder and stomach fistulas.

1. The removal of gastric juice reduces in normal dogs the sodium chloride concentration, but not the volume of the urine.

2. The removal of gastric juice in dogs treated with Novasurol decreases the diuresis and counteracts the increase of the sodium chloride concentration in the urine.

3. It is assumed that the shifting of the acid-base equilibrium toward the alkali side is due to the gastric juice removal which is the principal reason for the depression of the Novasurol diuresis.

## REFERENCES

1. ETHRIDGE, C. B., MYERS, D. B., AND FULTON, M. N.: The modifying effect of various inorganic salts on the diuretic action of salyrgan. *Arch. Int. Med.*, 57: 714, 1936.
2. FLIEDERBAUM, I., AND KRASUCKA, L.: Sur l'action diuretique synergetique des composés de mercure et d'ammonium. *Presse med.*, 40: 854, 1932.
3. GOLDRING, W.: Edema in congestive heart failure: effectiveness of diuretics as a guide to prognosis. *Arch. Int. Med.*, 44: 465, 1929.
4. MELVILLE, K. I., AND STEHLE, R. L.: Novasurol diuresis. *Arch. f. exper. Path. u. Pharmacol.*, 123: 175, 1927.
5. SCHOENHOLZER, G.: Mineralstoffwechsel und Quecksilberdiuresis. *Schweiz. med. Wehnschr.*, 69: 1321, 1939.
6. CLAUSSEN, F.: Quecksilberdiuresis. *Ztschr. f. d. ges. exper. Med.*, 83: 231, 1932.  
Idem.: Ueber die Diuresis des Herzkranken. *Ergebn. d. inn. Med. u. Kinderh.*, 43: 764, 1932.
7. EVANS, W. A., JR.: The effect of changes in salt and water metabolism on salyrgan diuresis, with special reference to the effect of permanent bile fistula. Medical papers dedicated to H. A. Christian. Baltimore, Williams & Wilkins Co., 1936, p. 204.
8. KEITH, N. M., AND WHELAN, M.: A study of the action of ammonium chloride and organic mercury compounds. *J. Clin. Investigation*, 3: 149, 1926.
9. SAXL, P., AND ERLSBACHER, O.: Ueber die Verstärkung der Novasurol (Salyrgan) Diuresis durch Ammonium-chlorid. *Wien. klin. Wehnschr.*, 42: 36, 1929.
10. ENGEL, K., AND EPSTEIN, T.: Die Quecksilberdiuresis. *Ergebn. d. inn. Med. u. Kinderh.*, 40: 187, 1931.
11. DRAGSTEDT, L. R., AND ELLIS, J. C.: Fatal effect of total loss of gastric juice. *Am. J. Physiol.*, 93: 407, 1930.
12. SCOTT, H. G., HOLINGER, P. H., AND IVY, A. C.: Demonstration of dog maintained for 16 weeks solely by jejunal alimentation in presence of loss of gastric juice. *Proc. Soc. Exper. Biol. & Med.*, 28: 569, 1931.
13. HABERLAND, H. F. O.: Die operative Technik des Tierexperiments. Wien, Urban u. Schwarzenberg, 1934, p. 332.



# CRANIOPHARYNGEOMA AND SUPRASELLAR ADAMANTINOMA\*

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## INTRODUCTION

In a brief report (1) published in 1923, one of us (J. H. G.) recorded the clinical and anatomical findings in a case of what he termed a teratoid cyst of the hypophysis, a type of a tumor which would now be termed craniopharyngeoma. Attention was then called to the fact that in the earlier days tumors of this type were described under a large assortment of names such as cholesteatomas, dermoids, epidermoids and occasionally, when cartilage was found among their histological contents, as teratomas.

The term cholesteatoma was first employed by Mueller (2), because of the presence of cholesterol crystals within such cystic tumors. This term, however, was rejected by Virchow (3) for in his experience such crystals were not uniformly present in such cysts. Moreover, he regarded these crystals as the product of a degenerative process and not at all distinctive of such tumors. He preferred the older designation of Cruveilhier (4) "Tumeurs Perlées" and was inclined to consider the pial and dural tissues as the source of these tumors. Rémak (5), in opposition to this view, regarded them as dermoids and therefore placed these tumors in the category of teratoids. Bonorden (6) described a cyst in which he found a stratified squamous epithelial lining and many spherical concentrically arranged collections of squamous epithelial cells, constituting structures simulating epithelial pearls. Underneath the epithelial cell lining, he found groups of sebaceous cells. These observations indicated the ectodermal origin of the tumor and led him to the conclusion that Rathke's pouch and the hypophyseal duct, at points of closure of the primitive medullary tube, are the probable source of origin of this type of tumor.

Among others who studied this type of tumor was Beneke (7). He, at first, because of the morphology of their cellular constituents as demonstrated with the aid of silver stains, considered these tumors as arising from the endothelial lining of the meninges. Subsequently, however, having found hair in some of these tumors, he revised his opinion and suggested an epidermal derivation for some and an endothelial for others.

Bostroem (8), studying the histologic character of the so-called cholesteatomas, decided in favor of their epidermoid nature and suggested their bigeminal origin, since they contained both mesodermal and ectodermal components. He, too, stressed the fact that in the course of the formation of the primary and secondary vesicles, histogenetic processes take place in enveloping mesoderm and ectoderm in areas adjacent to zones of constriction in the medullary tube. These sites favor embryonal misplacement of epidermis. Such cellular heterotopias, in his opinion, serve as the source of such tumor formations.

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It was Erdheim (9), however, who was able to identify with greater accuracy a separate group of these tumors, such as are found at the base of the brain in the vicinity of, and connected with, the pituitary body. Erdheim was aided in his study of these tumors by his previous successful investigation of epithelial cell remnants in the thyroid region in relation to the subinvolved thyroglossal duct. It led him to the search for similar cell remnants along the involuted hypophyseal duct. He found such cellular residues in about 77 per cent of normal adult pituitaries, usually plastered on the anterior surface of the proximal lobe. The cells in these small aggregations were of the squamous epithelium type exhibiting intercellular bridges and intracellular keratin granules. He came to the conclusion that the so-called cystic cholesteatomas; when associated

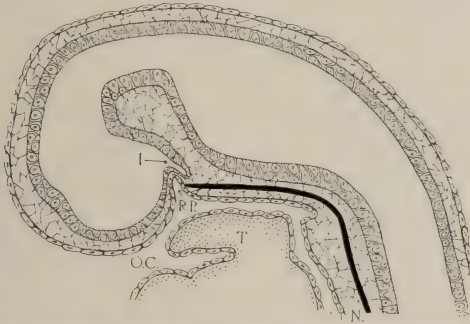


FIG. 1. Semi-diagrammatic drawing of a median longitudinal section of the head end of 11.4 mm. Pig embryo, showing R. P. (Rathke's pouch); I. (Infundibulum); O. C. (Oral cavity); N. (Notochord); and T. (Tongue). (After Jordan and Kindred.)

with the pituitary, took origin from the remnants of a subinvolved hypophyseal duct. He suggested for such cysts the term *hypophyseal duct neoplasms*.

Years later, Cushing (10) recommended the well adopted but somewhat inaccurate term craniopharyngeoma for this type of tumor. The inaccuracy will become evident when the embryogenesis of the hypophysis is reviewed.

The latter has two separate points of origin; an upward evagination of the embryonal oral cavity (fig. 1) [it is to be noted that it is not the pharynx that gives rise to this evagination which is to become the hypophyseal duct and subsequently Rathke's pouch—hence the inaccuracy of the term craniopharyngeoma], and a downward evagination from the floor of the third ventricle. The former gives rise to the anterior lobe of the pituitary while the latter to its posterior lobe. The accompanying figures 1 to 3 schematicize the stages in the development of the anterior lobe of the hypophysis, with particular emphasis on the origin and fate of Rathke's pouch and the hypophyseal duct. It will be noted that in the course of development the hypophyseal duct disappears,

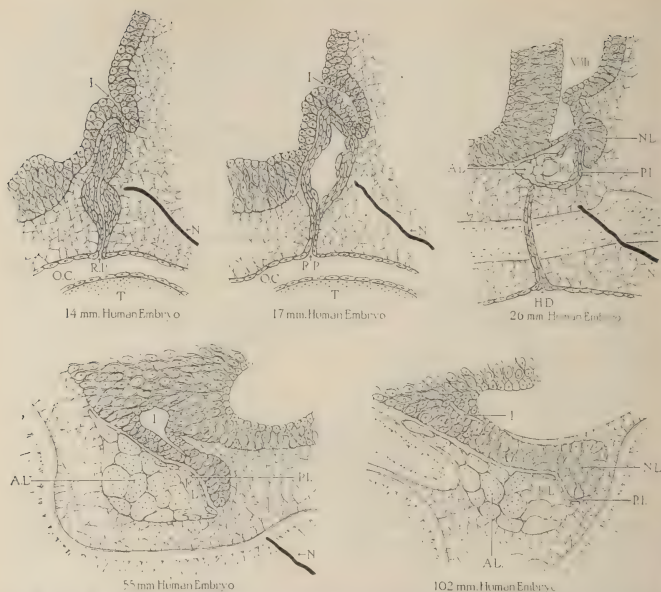


FIG. 2. Semi-diagrammatic drawing of a selected part of the head end in human embryo, showing the several stages in the development of the hypophysis and the gradual obliteration of the hypophyseal duct. R. P. (Rathke's pouch); O. C. (Oral cavity); I. (Infundibulum); N. (Notochord); T. (Tongue); H. D. (Hypophyseal duct); A. L. (Anterior lobe of the hypophysis); R. L. (Residual lumen of Rathke's pouch); P. I. (Pars intermedia of the hypophysis); N. L. (Neural lobe of pituitary); and V. III (Third ventricle). (Modified, from Atwell.)

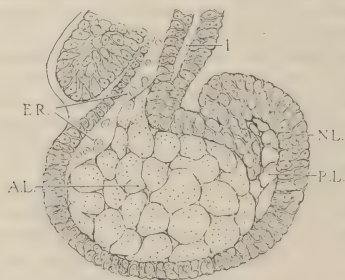


FIG. 3. Schematic drawing of the maturing pituitary, showing the location of the hypophyseal duct residues. E. R. (Epithelial rests); A. L. (Anterior lobe of the hypophysis); R. L. (Residual lumen); N. L. (Neural lobe); and I. (Infundibulum).

but leaves behind squamous epithelium residues which during the rotation of Rathke's pouch find their way to the surface of the infundibulum (fig. 3). Now that these residues can be definitely traced to the primordia in the oral cavity, it can be readily realized why tumors which have their origin in such embryonal rests may contain structures duplicating those found in the maturing oral cavity.

Following Erdheim's demonstration of the true origin of these tumors, cases such as fall definitely into this category were described under other names or without assigning a special name to them. This was particularly true of the case described by Farnell (13). Farnell, under the term of an extracerebral tumor in the region of the hypophysis, described what now appears to be an adamantinoma in which he found that "in the older portions of the tumor the cells have not only undergone horny changes, but have become infiltrated with lime salts and appear as 'abortive enamel prisms' as in a tooth."

However, soon other significant contributions made on the subject brought substantial proof of the accuracy of Erdheim's observations. Among these are those of Duffy (14), Crichtley and Ironside (15), Peet (16), Beckman and Kubie (17), Bailey (18), Globus (1), Frazier and Alpers (19), and MacCallum (20).

#### CASE REPORTS

In presenting the clinical and anatomical survey of the fourteen cases to be described, it was found advisable to divide them into two subgroups, 1) the cystic and 2) the solid tumors. In all probability the difference in the consistency of the tumors is dependent upon the character of the primordial material from which the individual tumors are derived. This, in turn, will justify the adaptation of a simplified terminology and classification of tumors commonly grouped with the craniopharyngeoma and adamantinoma.

*Case 1. Cystic hypophyseal duct tumor (craniopharyngeoma) in a girl, aged 6 years. Vegetative disturbances: obstinate constipation, anorexia, polydypsia, polyuria, fatigability, insomnia, infantilism. Mental regression, general and focal signs of an expanding intracranial lesion. Transfrontal craniotomy, retrochiasmal suprasellar cyst found; operation interrupted, exitus.*

*History:* L. P., (P.M. #3713), a girl, aged 6 years, had no previous illness and was said to have been quite normal up to the time of the onset of the final illness. Six months before admission to the hospital, she became markedly constipated. She did not sleep well, became restless, lost her appetite and was constantly thirsty. The diagnosis of diabetes was made, and the child was treated accordingly. With the increase of thirst and water intake, there was a corresponding increase in volume and frequency of urination. The child was losing strength, and would frequently complain of fatigue and stop playing. She became irritable, subject to constant headache and finally became confined to bed because of general weakness. A week before admission, it was noted that the child's mouth was drawn to one side, and her left shoulder twitched frequently and drooped.

*Examination:* The patient was somewhat undersized, with a profuse growth of lanugo hair all over her body. There was ptosis of the right eyelid and an external strabismus of the right eye. The left pupil was larger than the right, both pupils reacting to light and on convergence. There was a left facial paresis and slight weakness of the left upper extremity, which was held in the hemiplegic position. There was also slight weakness of the left leg. The deep reflexes were more active on the left side, though generally reduced.

A doubtful Babinski sign was present on the left side. The abdominal reflexes could not be elicited.

*Laboratory data:* Urine had a low specific gravity, and acetone and diacetic acid were present on repeated examinations. Lumbar puncture yielded clear fluid under increased pressure. X-ray examination of the skull showed marked enlargement of the sella turcica, and evidence of increased intracranial tension.

*Course:* Transfrontal craniotomy was done, and a bluish mass was found to the inner side of the right optic nerve. The mass was behind the pituitary. Operation was interrupted because of poor condition of the patient. She died within a few hours.



FIG. 4. (Case 1). Base of the brain showing craniopharyngeal duct cyst (craniopharyngoma) in the interpeduncular space. It is partially collapsed and rostrally adherent to the optic chiasm.

*Necropsy findings. (Brain examination only permitted) GROSS:* The pia-arachnoid was markedly edematous and of a purple hue. The convolutions of the brain were markedly flattened. A large purple, fluctuant mass was present at the base of the brain (fig. 4). It covered the optic chiasm, to which it was adherent, and filled up the entire interpeduncular space. Its bulging inferior and partially free surface was prolonged into a funnel-shaped process, which seemed to be continuous with the pituitary body. The dorsal surface of this mass was firmly implanted in the substance of the brain. The optic chiasm and tracts were flattened.



The tuber cinereum and the mammillary bodies could not be identified since the floor of the third ventricle was stretched and flattened by the tumor mass, which almost obliterated the cavity of the third ventricle. The cerebral peduncles were displaced laterally and were reduced in size. This was particularly pronounced on the right side. During the process of detachment of the brain from the base of the skull, the neoplasm was punctured and a dark brown, granular, semi-fluid mass escaped from the cavity. On opening the latter more fully, it collapsed, and it was then noted that it was a rather thin walled cyst, lined

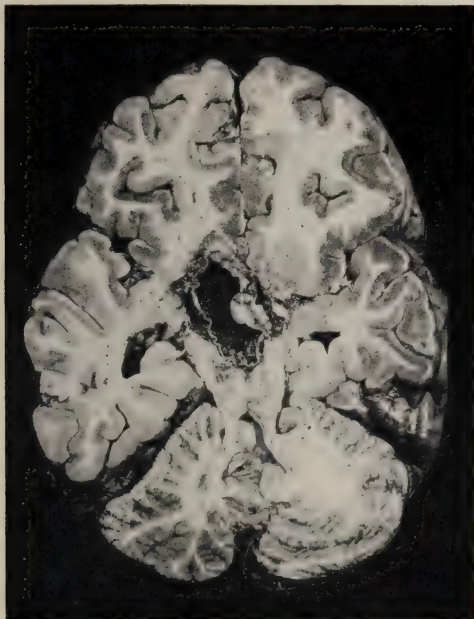


FIG. 5 (Case 1). Hypophyseal duct cyst showing a cartilagenous nodule in its wall.

by a corrugated membrane which was studded with numerous small, glistening elevations. Cholesterol crystals were demonstrated in the contents of the cyst. The cyst was 4 cm. in length and about 3.5 cm. in width. It had markedly stretched the vessels constituting the circle of Willis, particularly the posterior communicating and anterior cerebral vessels.

The third nerve on the right side was compressed and flattened by the neoplasm. A horizontal, longitudinal section of the brain gave a still better view of the gross structural changes that were brought about by the neoplasm. The cavity of the cyst was fully exposed and its inner wall was disclosed. The lining of the cyst gave the appearance of a mucous coat. At the left anterior portion of the cyst, the wall was thickened, giving rise to a tuberos elevation, cartilagenous in consistency, and somewhat translucent in appearance (fig. 5).

The *pituitary body* was extremely small in size, compressed and lodged in a shallow sella turcica.

*Microscopic observations:* The cyst was of fairly uniform thickness, except for a small part in which there was present a nodule of cartilaginous consistence, and in its major portion was composed of three fairly distinct layers. Its lining or innermost coat was a thin sheath of stratified squamous epithelium, which exhibited in various parts slight

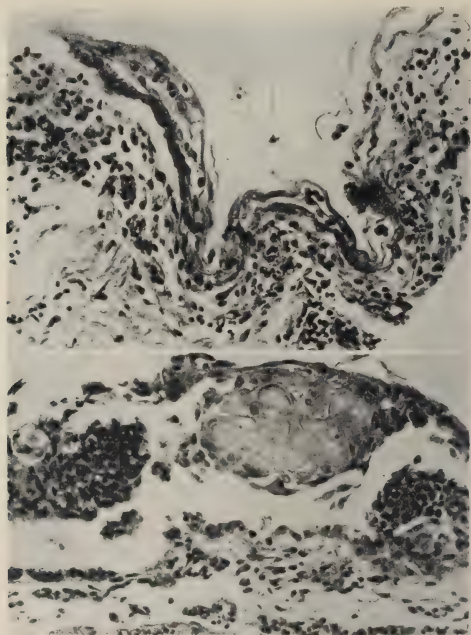


FIG. 6a (Upper) (Case 1). Section of the cyst wall showing the primitive stratified epithelial lining. Hematoxylin and eosin stain.

FIG. 6b (Lower) (Case 1). Section of the cyst wall showing a collection of hornified epithelial cells with structures simulating hair follicles on either side of an epithelial pearl. Hematoxylin and eosin stain.

variations indicating stages in the development (fig. 6a). The next or middle layer consisted of loose connective tissue which contained here and there a few glandular structures and small ducts. The acini bore a strong resemblance to those in sebaceous glands, while the ducts were lined with tall cuboidal epithelium, and their lumen was filled with pink-stained colloidal substance. The outermost layer was in the nature of a thin but fibrous capsule.

The innermost layer of the squamous epithelium as already suggested had retained the features of embryonal dermis. Within it could be recognized the three primitive layers:

the epitrichium, the intermediate layer and the lowermost layer, the striatum germinativum. At some points there were visible cellular collections within the germinal layer which had the appearance of hair primordia (fig. 6b). In adjacent parts there were seen accumulation of deeply staining large, epithelial cells arranged in concentric fashion simulating epithelial pearls. All of the cells displayed some degenerative changes. Although the cells at the periphery retained some of the characteristics of the basal cell epithelium, those in the center of the pearls had undergone complete hyalinization. When special stains were applied (iron hematoxylin) the intercellular bridges of the former could be demonstrated; when stained with Weigert's keratin stain, a blue color was imparted to these cells, establishing the presence of keratohyalin granules (fig. 7).

The small, cartilaginous in consistence, mass revealed several histologic structures of mesodermal origin, such as embryonal cartilage (fig. 8), mucous connective tissue, mesenchymatous tissue, newly formed bone (fig. 9) with fairly typical bone corpuscles, calcified

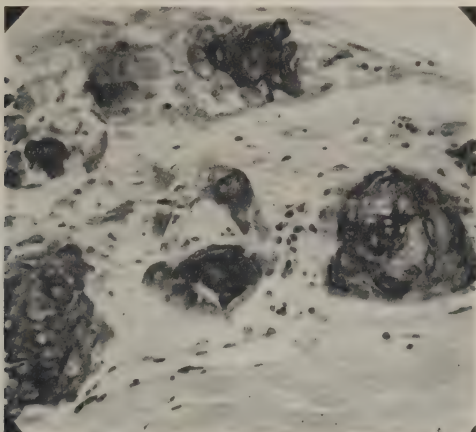


FIG. 7 (Case 1). Section of the cyst wall showing a collection of hornified and keratinized epithelial cells. Iron hematoxylin and eosin stain.

trabeculae, endosteum and periosteum, displaying osteoclasts and osteoblasts, marrow cells with yellowish granules giving characteristic iron reaction. There were also a collection of cells arranged in a long cord and supported by a fine connective tissue showing, when stained for fat, irregularly distributed fine fat granules (fig. 10). Their true character could not be ascertained. Whether they were embryonal fat cells or cells of the category found in sebaceous glands remained a question.

*Comment:* This case was selected as the first to be described in this series because it presents typical clinical manifestations and characteristic histological features. The combination of vegetative disturbances, such as obstinate constipation, anorexia, polydipsia and polyuria, when added to evidence of dyspituitarism (infantilism) and to the general signs of increased intracranial tension and focal signs arising from the implication of the brain stem, pointed

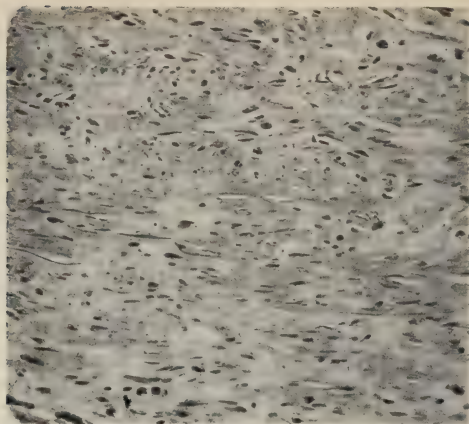


FIG. 8 (Case 1). Section of the cartilaginous nodule within the wall of the cyst showing young cartilage cells. Hematoxylin and eosin stain.

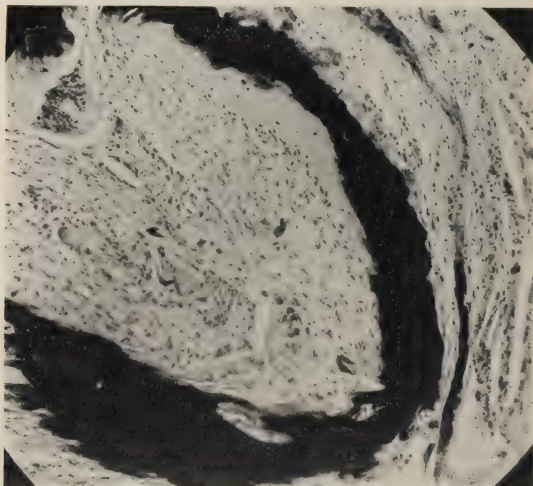


FIG. 9 (Case 1). Section of the cartilaginous nodule showing a layer of calcified bone with periosteal and endosteal tissue containing foreign body giant cells and cholesterol crystal spaces. Hematoxylin and eosin stain.

definitely to an expanding lesion within the interpeduncular space. The age of the patient favored the probability that the tumor was of the nature of a hypophyseal duct neoplasm.

Anatomically the tumor belonged distinctly to the cystic variety which Duffy (12) would group with the benign squamous epithelial cysts and which Cushing (10) had named craniopharyngeoma. The latter term has been accepted although there are some justifiable objections to it, in that the actual origin of the so-called craniopharyngeal duct remnants which gives rise to such tumors is not really in the pharynx but in the oral portion of the stomodeum. Of particular interest in this case was also the presence of structures which

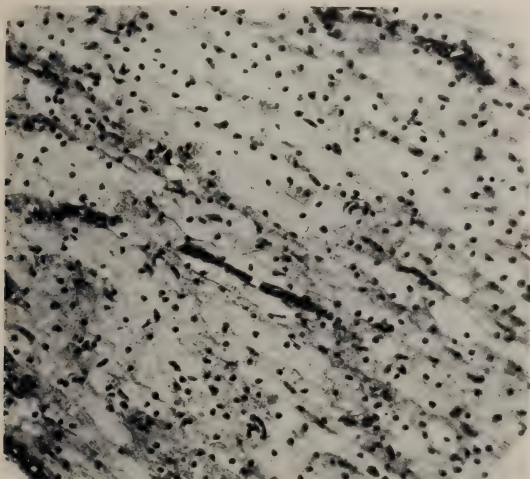


FIG. 10 (Case 1). Section of the cartilaginous nodule showing a collection of sebaceous gland cells. Iron hematoxylin and eosin stain.

indicate the bigeminal origin of the tumor, placing it as was originally done (1), among the autochthonous teratoid cysts.

*Case 2. Cystic hypophyseal duct tumor (craniopharyngeoma) in a boy, aged 3½ years. Sudden onset following alleged injury to the head, followed in order of occurrence by recurrent headaches, ocular palsies, frequent vomiting, periodic somnolence; polydipsia and polyuria, uncinat fits, optic atrophy, and endocrine disturbances of the hypopituitary character. Bitemporal visual field defect with diminution of acuity of vision. Calcifications in a deep sella turcica, dissociation of pulse and temperature curves. Exploratory craniotomy, suprasellar part of a cystic tumor removed. Stormy convalescence, good recovery; patient free of symptoms for 2 years, re-entered the hospital for an acute ear infection. Ligation of jugular vein. Exitus.*



*History:* J. B., (P.M. #8719) a boy, aged  $3\frac{1}{2}$  years, had met with an accident at the age of 3 years. He fell three short steps, sustaining no obvious injury and exhibiting no immediate sequelae. Three months later, he began to complain of headaches. They would begin about 10:00 a.m. and persist for a period of four hours. As the headache would subside, the patient would appear to be alert and return to play. At about the same time, it was noted that his left eye became smaller than the right and that the left eye was turned outward. Two months later he began to complain of epigastric pain, usually following the headaches. The pain was relieved by vomiting, which was usually followed by sleep of an hour or more. On awakening, the patient would be free of any discomfort and become active and playful again. In the course of that month, he lost about 10 pounds. It was noticed that during that period, he began to complain of thirst and drink more frequently. He also would experience peculiar smells which he described as "bad" and which no one else in the room could detect.

*Examination:* The only positive findings included the following: moderate pallor of the discs, especially of the left; a slight left central facial weakness; a slight weakness of the left extremities; an equivocal left plantar response; and endocrine features described as of the hypopituitary type. Visual field examination revealed a definite diminution in range and facility of vision on the left with a definite temporal field defect on that side.

*Laboratory data:* X-ray examination of the skull revealed a markedly deepened sella turcica; marked erosion of the posterior clinoids; several small calcific concretions within the sella turcica and some above the sella turcica. There was also evidence of increased intracranial pressure.

*Course:* The diagnosis of a tumor in the sellar region was made. While under observation, it was noted that the occasional moderate rise in temperature was not followed by increasing rise in the pulse rate. In fact, with a rise in temperature, the pulse usually became lower, and became more rapid when the temperature fell. This was not regular in occurrence.

He was subjected to an exploratory craniotomy for suspected craniopharyngeoma. A two stage transfrontal operation was performed and the sella turcica was exposed. The entire suprasellar portion of the tumor was removed. Following the operation, there was at first a sudden rise in temperature which gradually came down to normal. It continued to be somewhat elevated and again showed a discord between the pulse rate and the temperature curve. Otherwise, the convalescence was rather smooth and at the end of eight weeks, six weeks after the operation, he was up and about and allowed to return home. However, the pallor of the left disc seemed to increase and now there appeared a pallor of the right disc.

*Interval history:* The patient remained free of symptoms for a period of two years. Five weeks before readmission to the hospital, he complained of pain in the right ear. There was no discharge from the ear. At about this time, he developed measles which lasted about 10 days. Shortly thereafter, he again complained of pain in the right ear. This time the temperature rose to  $104^{\circ}\text{F}$ . A physician performed a myringotomy and evacuated some pus. The patient continued to run a septic temperature and vomited several times. Five days before readmission to the hospital, he passed through a convulsive episode which lasted about 30 minutes. Shortly before entering the hospital, he complained of pain back of the ear.

*Second admission:* On admission, the child was found to be rather obese, exhibiting a pituitary habitus of the Froelich type, and the right ear showed a pulsating discharge through a postero-inferior perforation. There was slight mastoid tenderness on the right side. Bilateral optic atrophy more pronounced on the right side, depressed tendon reflexes and bilateral Oppenheim and Babinski signs were the significant neurological findings. The patient's temperature continued to be septic and elevated to  $106^{\circ}\text{F}$ . A jugular vein ligation with packing of the right transverse sinus was performed. Following the operation, the patient had four convulsive seizures and died 17 hours later.

*Necropsy findings.* *Brain.* *Gross:* The brain was swollen and edematous. Numerous

fine adhesions were present in the right frontal region between the pia-arachnoid and the dura mater. These were also present in the right cribriform region. The right olfactory nerve was absent; the left was well demonstrated. In the interpeduncular region there was seen a large cystic tumor mass measuring about 2.5 cm. in diameter. On either side of this mass the optic nerves were flattened and displaced. The meninges and blood vessels were otherwise negative.

On freeing the brain from the sphenoid bone, the cyst (fig. 11) was found occupying the entire interpeduncular space and extending forward toward the cerebral hemispheres and

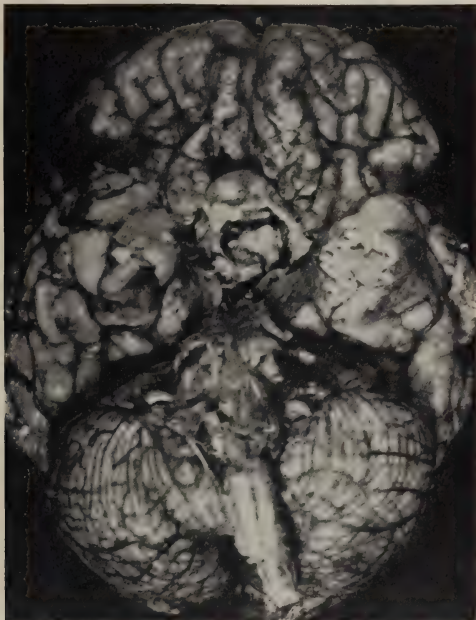


FIG. 11 (Case 2). The base of the brain displaying the large cyst in the interpeduncular space.

underneath them. The cyst was thin walled and contained greenish yellow material with pockets filled with a gelatinous substance. It was adherent to the walls of the sella turcica. The sella turcica was exceedingly deep (about 1.5 cm. in its depth).

On sectioning the brain, a moderate symmetrical internal hydrocephalus was found.

*Microscopic observations:* Sections of the cyst, stained with hematoxylin and eosin, revealed a band of distorted connective tissue, lined by a thin layer of closely packed stratified squamous epithelial cells (fig. 12a). At one edge of the section there were cells with large oval vesicular nuclei (fig. 12b), extending about 8 rows in depth supported by a

basement membrane of a single row of columnar epithelium. Near this area there was a collection of calcified lamellated bodies and hornified epithelial cells surrounded by endothelium cells. The adjacent fibrous tissue contained many round cells, multinucleated giant cells and calcified blood vessels.

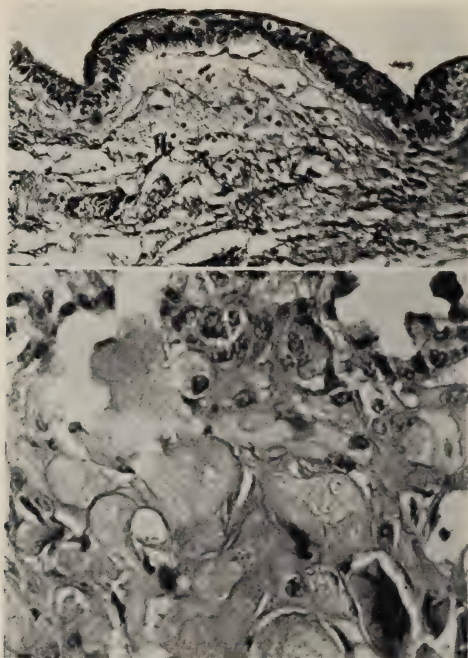


FIG. 12 (Upper) (Case 2). Section of the cystic wall showing the stratified squamous epithelial lining. Hematoxylin and eosin stain.

FIG. 12b (Lower) (Case 2). Collection of degenerating epithelial cells. Hematoxylin and eosin stain.

*Comment:* Of interest in this case is the fact that the clinical manifestations pointing to the presence of an expanding intracranial lesion had their beginning at the early age of 3 years. It may be assumed that the development of the tumor preceded the onset of clinical signs and symptoms. The fact that an accident had occurred, without any obvious serious injury to the head, shortly before development of symptoms, does not bring into causal relationship the alleged injury with the development of the tumor or related symptoms. In

this case the deep sella turcica, the erosion of the posterior clinoids, the calcific concretions within and above the sella turcica, and other evidence of increased intracranial pressure placed the lesion in the sellar region, but the dissociation of pulse and temperature curves could be considered as a leading diagnostic sign pointing to implication of the hypothalamus. Although the patient did well after the first operation and died of an intercurrent infection, on the basis of experience with other similar cases, it may be assumed that this young patient would not have escaped recurrence of symptoms and a final fatal termination.

*Case 3. Cystic hypophyseal duct tumor (craniopharyngeoma). Onset at the age of 13 months with a rise in temperature and convulsive seizures followed by paralysis of the left abducens nerve, general weakness and loss of weight. Excessive thirst with polydipsia and polyuria followed. At the age of 3 years another febrile episode with convulsions followed by a 5 day period of coma. Subsequently, temporary loss of vision; bilateral primary optic atrophy, absent deep reflexes; calcific areas above enlarged sella turcica. Craniotomy, cyst in the interpeduncular space punctured and curetted, followed by recovery. One year later, polydipsia and polyuria, and protracted somnolence with return of headaches. Continued observations for 6 years, patient exhibiting progressive decline.*

*History:* C. C., (Surg. #60278), a Spanish girl, aged 3½ years, was admitted to the hospital on August 2, 1937. At the age of 13 months, she developed a febrile illness accompanied by convulsive seizures. While convalescing, three or four weeks later, it was noted that her left eye was turned out and that the child acted as if she did not see well, bumping into objects. She appeared to be weak, and lost weight. Her legs progressively assumed a valgus deformity. She developed excessive thirst, drinking five to six quarts of fluid a day, and marked polyuria. At the age of 3 years, she again developed fever and convulsions. She was hospitalized and treated with bromides and intravenous fluids. Following one of these convulsions, she became comatose for a period of five days. When she regained consciousness, it was discovered that she was almost completely blind. The blindness receded gradually so that at the time of admission she could see quite well.

*Examination:* The patient was a bright alert female child of 3½ years. Blood pressure was 70 systolic and 50 diastolic. There was bilateral primary optic atrophy, more marked on the left side, and some weakness of the left superior rectus muscle. Vision in the right eye was 5/20; left eye, 3/200. Both knee jerks and the left ankle jerk were absent. The abdominal reflexes were active.

*Laboratory data:* Urine, blood cytological and blood chemical studies were negative. X-ray examination of the skull showed the sella turcica to be increased in its antero-posterior diameter and in depth. There were numerous areas of calcification in the supra-sellar region and to the right of the sella turcica. There was slight separation of the frontal sutures.

*Course:* A neoplasm in the region of the pituitary body was diagnosed but, because of fever, surgical intervention was deferred until August 23, 1937. At that time a fronto-temporal flap was made, the frontal lobe retracted and a cyst medial to the optic nerve was found; it was punctured and curetted. Following the operation, the child developed a left sided weakness, which gradually disappeared. Vision improved remarkably, her temperature returned to normal and her water intake and output regained a normal level.

*Surgical specimen:* A section of scrapings of tissue taken from the cyst wall, stained with hematoxylin and eosin, revealed an irregular band of stratified squamous epithelial cells covering many spherical collections of hornified and some calcified epithelial spheres (fig. 13). There was also a background of poorly staining collagenous fibrous tissue. A few capillaries and a small area of hemorrhage were present. The diagnosis was that of craniopharyngeoma.

*Second admission:* (October 25, 1938). The patient was readmitted about a year after the operation, mainly because of the return of polydipsia and polyuria. These disturbances



in water balance were partially controlled by intranasal administration of pituitrin. At about the same time, the patient developed somnolence, sleeping longer in the afternoon than she formerly had been doing.

On admission, it was found that the optic nerves were pale and that she had moderate weakness of the left arm and leg, and depressed deep reflexes. Radiotherapy in the region of the sella turcica, accompanied by intranasal instillation of pituitrin resulted in moderate improvement. Areas of alopecia developed at the site of the x-ray exposures and the radiotherapy was stopped.

*Third admission: (April 3, 1941).* Since her previous admission, headache recurred every few weeks, lasting several hours, and was accompanied by drowsiness. Polydipsia and polyuria were present during the interval of almost one and a half years. At this time both discs were found to be white with very clearly defined margins. There was general hyporeflexia with some weakness of the upper and lower extremities. During her stay in the hospital, she passed through a period of semi-stupor and vomiting. Surgical intervention was considered inadvisable.

She was seen in the Follow-up Clinic on January 5, 1943 and found to be apathetic and showing evidence of further decline. The polydipsia and polyuria were increasing. Patient has not been seen since that date.

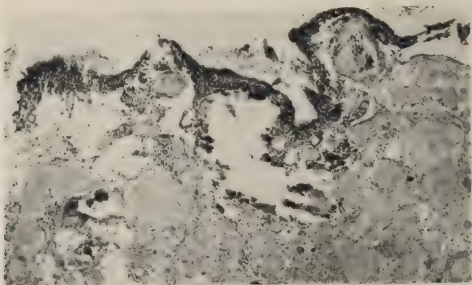


FIG. 13 (Case 3). Section of the surgical specimen removed at the first operation displaying a band of stratified squamous epithelial cells overlying spherical collections of hornified and calcified epithelial cells. Hematoxylin and eosin stain.

*Comment:* This case of a child of 3½ years had already presented the frank manifestations of a suprasellar tumor when only 13 months, with symptoms which in retrospect could be regarded as early manifestations of this type of tumor formation. Of particular significance were the manifestations of hypothalamic disorder, polydipsia and polyuria, elevation of temperature and convulsions. Histologically the tumor was clearly of the kind described as craniopharyngeoma or stratified squamous epithelial (papillary) cyst of the hypophyseal duct.

*Case 4. Cystic hypophyseal duct tumor (craniopharyngeoma with adamantinomatous islands) in a boy aged 10½ years.* Onset with visual impairment, headaches, endocrine disturbances, attack of abdominal distress. Appendectomy. Subsequent development of meningeal signs. X-ray examination of skull revealed calcification in the suprasellar region. Craniotomy, prechiasmatal cyst found. Aspiration with partial excision. Rapid decline and exitus.

*History:* M. B., (P.M. #9024), a boy, aged 10½ years, had noticed failing vision for six months before admission, and had complained of occipital and frontal headaches for two



months. He was seen once in the Endocrine Clinic of the Out Patient Department because of these symptoms and obesity. Five weeks before admission, he complained of nausea and vomited without experiencing abdominal pain. On December 28, 1933, one day before his entering the hospital, he was suddenly seized with abdominal pain, which was most marked in the right lower quadrant and was accompanied at first by vomiting.

The patient was markedly obese with an excessive deposit of fat about the hips, breasts and genitalia. He displayed underdeveloped secondary sex features. There was tenderness and rigidity in the right lower quadrant. The white blood cell count was 11,600 with 87 per cent polymorphonuclear leucocytes. The temperature was 100°F.; the pulse rate, 80 per minute. The diagnosis of acute appendicitis was made.

Appendectomy was performed and an acutely inflamed appendix was removed. Twenty-six hours later his temperature was 100.2°F. and pulse, 132. He complained of headache. Neck rigidity with some limitation of forward flexion of the head and suggestive bilateral Kernig sign were observed. A lumbar puncture revealed clear cerebrospinal fluid under normal pressure, containing no cells. The nuchal rigidity and bilateral Kernig sign became more pronounced. Further study disclosed a bilateral Babinski sign, depressed deep tendon reflexes, advanced bilateral papilledema with retinal hemorrhages, diminished visual acuity in the right eye and a suggestive temporal defect in the left. There was moderate dulling of intellect. The blood pressure was somewhat elevated, 142 systolic and 94 diastolic.

X-ray examination of the skull revealed erosion of the posterior clinoid processes, thinning of the dorsum sellae, and linear calcification just outside of the sella turcica, at about the level of the posterior clinoids, interpreted as "calcification in a Rathke Pouch Tumor."

The patient became progressively more stuporous. A craniotomy was done. At operation, a cystic mass was found in the prechiasmal region. It was aspirated and then partially excised. The patient did not react well post-operatively and his temperature rose rapidly. He died on the second day after the operation.

*Necropsy findings. Brain. Gross:* The cerebral convolutions were flattened; the olfactory bulbs were slightly distorted and traumatized. The optic nerves and chiasm were edematous. The gyri recti were fused in the prechiasmal region. Below and behind the optic chiasm, there was a cystic tumor mass extending to the belly of the pons (fig. 14). The floor of the third ventricle was obscured by the cyst and the dark hemorrhagic fluid contained within it. The posterior clinoid processes and dorsum sellae were eroded and thinned.

On sectioning of the brain, the lateral ventricles were seen to be markedly and symmetrically dilated. The third ventricle was somewhat larger anteriorly. In front of the middle commissure all that was left of the tumor was a segment of its wall situated directly inferior to the anterior portion of the floor of the third ventricle. It was adherent to the optic chiasm which was somewhat flattened. The cerebral peduncles adjacent to the interpeduncular space were moderately disorganized. The third ventricle communicated directly with the remnants of the cyst. The oculomotor nerves were displaced posteriorly and laterally.

The *pituitary body* was found attached to the tumor. The cyst wall was markedly compressed and showed some cavitation.

*Microscopic observations:* Section through the wall of the cyst displayed a lining which consisted of stratified squamous epithelium of the embryonal variety (fig. 15a). It covered a layer of loose connective tissue. Within this connective tissue, there were seen islands of cellular material of varying types. In one part there were papillary projections covered by a layer of columnar cells simulating ameloblasts (fig. 15b). Deeper within this structure, there were collections of hornified epithelium and here and there little alveolar structures lined by columnar epithelium. Stellate cells were also found within this region. In other parts, there were hyalinized and hornified stratified epithelium; some were arranged in long bands and others in round collections (fig. 16a). Giant cells were frequently encountered. In another part, the tissue was made up of dense fibrous material interrupted by spaces such as are often seen around cholesterol crystal collections (fig. 16b).

*Comment.* In this case the endocrine disturbances very likely have proceeded the development of signs of increased intracranial tension. Were it not for the surgically verified existence of an acute appendicitis, the abdominal distress could be regarded as part of the hypothalamic disorder. The signs of meningeal irritation are not uncommon in tumors of this type, in all probability due to the escape of some of the contents of the cyst into the subarachnoid space. The



FIG. 14 (Case 4). The base of the brain showing the partially collapsed cyst in the interpeduncular space.

histological picture of that tumor requires no comment beyond the statement that it falls fully in the category of the cystic tumors of the hypophyseal duct.

*Case 5. Cystic hypophyseal duct tumor (craniopharyngeoma) in a girl aged 11 years, observed for four years. Patient exhibited signs pointing to anatomic disturbances within the interpeduncular space. Craniotomy; cyst found within the interpeduncular space; exitus.*

*History:* H. D. (P.M. #13025), aged 15 years, has had four admissions to the hospital. She had been underweight until one year before her first admission, when she began to put on weight rapidly so that within eight months she had gained 30 pounds. There was a coincident increase in appetite and thirst (she drank about 18 glasses of water and two glasses of milk daily). About eight months later, she had a sudden attack of pain in the frontal

region over the left eye which was accompanied by nausea. This episode lasted about four hours and recurred every two or three weeks. Within the last two weeks, there has been constant pain in the left frontal region of a dull character, as well as pain in both eyes, more so in the left. She complained of pain on looking upward and of diplopia when looking to the right. She was becoming more somnolent.

*Examination:* (First admission, September 19, 1940). The patient was an obese negro girl with slender extremities and fat distributed chiefly over the chest and abdomen. The gait

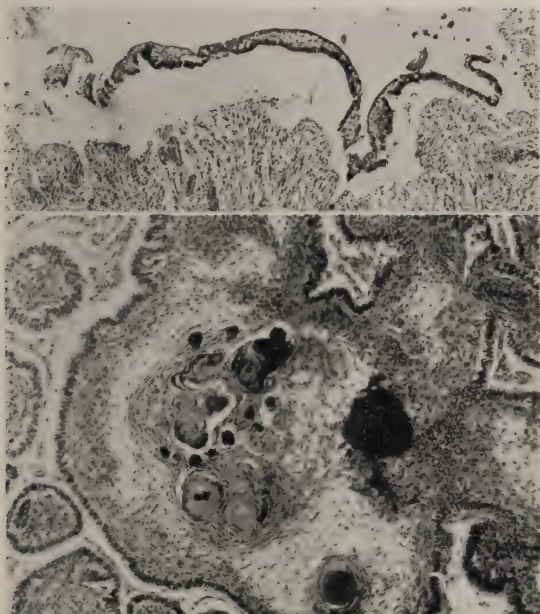


FIG. 15a (Upper) (Case 4). Section of the wall of the cyst showing a thin layer of stratified squamous epithelium, partially separated from the underlying supporting connective tissue. Hematoxylin and eosin stain.

FIG. 15b (Lower) (Case 4). Section of a thicker part of the cystic wall showing a solid collection of cells, the free surface of which is lined by columnar epithelial cells. Within its depth, it displays collections of hornified epithelium. Hematoxylin and eosin stain.

was normal but there was some diminution in associated movements of the right arm. The left pupil was dilated and fixed. There was ptosis of the left lid and some proptosis of the left eyeball. All movements of the left eye except on left lateral gaze were limited. The left corneal reflex was diminished. There was bilateral slight papilledema and fullness of the veins (left more than right). A mild right supranuclear facial paresis was present. Muscle power was good except for slight weakness in the right upper extremity. There were no sensory changes. The deep reflexes were generally depressed; the

left ankle jerk more so than the right; the right abdominal reflexes were absent, while those on the left side were active.

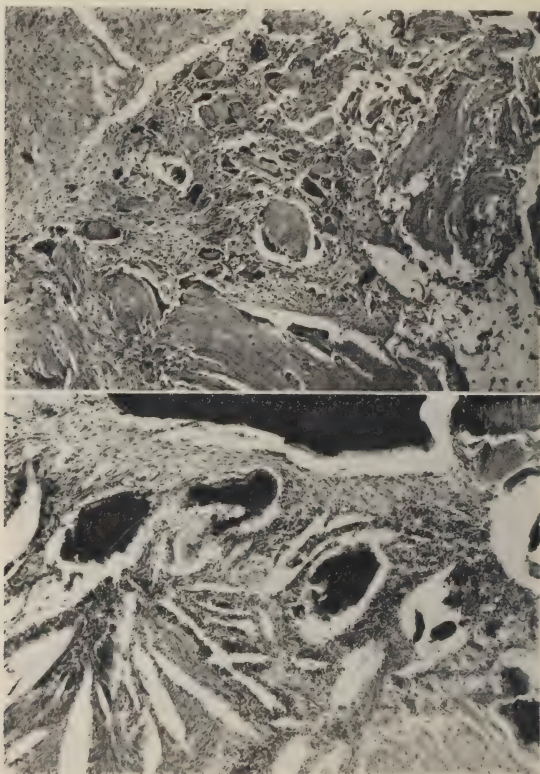


FIG. 16a. (Upper) (Case 4). Section of a thicker portion of the cyst showing long strips of hornified epithelium and an occasional foreign body giant cell. Hematoxylin and eosin stain.

FIG. 16b. (Lower) (Case 4). Section of a thicker layer of cyst wall showing small masses of calcified bone and free surfaces resulting from the dissolution of cholesterol crystals. Hematoxylin and eosin stain.

*Laboratory data:* Urine, normal. Blood: cholesterol, 355 mg. per cent; esters, 210 mg. per cent; urea nitrogen, 16; phosphorus, 5.2; calcium, 12.0; total protein, 7.7. The basal metabolic rate, minus 28 per cent (first test). The Wassermann reaction, negative. The Janney test, negative. X-ray examination of the skull disclosed an enlarged sella turcica with



irregular flocculent calcification extending from the floor of the sella upwards for about  $1\frac{1}{2}$  inches. There was some decalcification of the dorsum sellae and of the posterior clinoid processes. Laminographic x-ray study of the skull gave no additional evidence. X-ray examination of the chest and long bones showed no abnormal findings. Electroencephalography indicated increased intracranial pressure but not the presence of a cortical lesion.

*Course:* Shortly after her admission to the hospital, there was noted a partial left sided ptosis and fixed pupil with paresis of the eye movements in upward, downward and inward directions. Three days later, there was an obvious external strabismus and a dilated fixed pupil on the left side. A provisional diagnosis of craniopharyngeoma had been made, and three weeks later, a left transfrontal craniotomy was performed under local anaesthesia. A cyst (craniopharyngeoma) was found to occupy the interpeduncular space and to encroach slightly upon the chiasm beneath its posterior border. The contents of the cyst were evacuated and part of its wall removed.

*Surgical specimen.* *Gross:* Several small fragments of tissue suspended in saline received for study.

*Microscopic observations:* The surgical specimen after centrifuging and staining with hematoxylin and eosin presented several small fragments of tissue consisting chiefly of dense bands or whorls of hyalinized epithelium. Scattered through some of the stratified, pink-staining tissue could be seen small, round, dark-staining nuclei. No nerve elements were identified by the Nissl method.

*Diagnosis:* The presence of hornified epithelium was confirmatory of a craniopharyngeoma.

*Second admission:* The patient was readmitted on October 17, 1943, about three years after operation, with the account that she was doing well until September 29, 1943, when she suddenly passed through an episode of unconsciousness followed by vomiting. Several days later she had another seizure, now accompanied by a convulsion. Examination, at this time, revealed on lumbar puncture an increase of intracranial pressure, and no other findings of significance.

*Third admission: (August 11, 1944).* This time her admission was preceded by frequent bouts of vomiting. Examination yielded few positive findings. She was obese; there was some ptosis of the left eye; the deep reflexes were increased.

The cerebrospinal fluid was under increased pressure, and the total protein was 85 mg. per 100 cc. The electroencephalogram was interpreted as typical of idiopathic epilepsy. Encephalography showed dilated lateral and third ventricles.

She was subjected to revision of surgical field. A large cyst was found in the interpeduncular space. It was opened and curetted. Convalescence was satisfactory and the patient left the hospital sixteen days later.

The surgical material was reported as containing particles of hornified material and an occasional giant cell imbedded in necrotic tumor. The diagnosis again was craniopharyngeoma.

The patient was seen in the Follow-up Clinic on December 5, 1944. Her mother reported that the child slept most of the time and became subject to frequent fainting spells. They were preceded by violent headaches.

*Fourth admission:* She returned to the hospital on December 9, 1944. At this time an examination disclosed the following: left pupil fixed to light; left abducens nerve paresis; a right central facial weakness; a slight weakness of right upper extremity; slight increased deep reflexes in the lower extremities; Hoffman and Babinski signs on the right with absence of abdominals on the right; and some awkwardness in moving the right upper extremity. Operative intervention was seen to be hazardous and inadvisable so she was subjected to radiotherapy, for a period of two weeks. No change in her clinical manifestations was noted until December 28, 1944, when she had an attack, preceded by a cry with retraction of the head; she became unconscious; the right side of the body was spastic, deep reflexes of both upper extremities were absent, right lower hyperactive and the left lower diminished; but on both sides there was ankle clonus. Her pulse was 56; blood pressure, 102 systolic and



82 diastolic. Her head and eyes remained in lateral rotation and extension to the left, both pupils fixed, the left greater than the right. A deep stupor followed this attack and continued until her death on January 4, 1945.

*Necropsy findings. Brain. Gross:* A tumor was found overlying the sella turcica, bulging mainly to the left side. It occupied completely the interpeduncular space and extended back to the cerebello-pontine angle. It was covered by a smooth membrane through which could be seen a yellow white granular appearing material. Rostrally, just behind the optic chiasm, which was enveloped by the tumor, there was a small solid nodule of tumor tissue. The sella turcica was flattened out and greatly widened. The *pituitary* was also flattened from above downwards and a small fragment of tumor seemed to rise from the infundibular stalk.

On reflecting the arachnoid over the tumor, the latter was found to be mainly in the nature of a sac which seemed to narrow as it descended toward the left pontofacial angle. On careful dissection, the lower end was found to be readily separable from the underlying

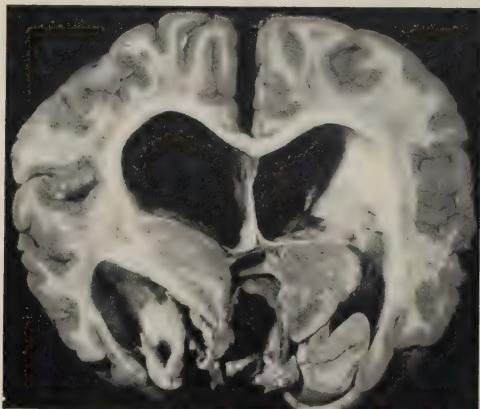


FIG. 17 (Case 5). Coronal section of the brain showing marked bilateral internal hydrocephalus and the third ventricle almost completely occupied by the cyst.

pons. At this point, it gave the impression of being little more than an extension of the main sac with the adhesions to the underlying structures. Also at this point, the sac was very thin but here and there, there were discernible small nodular masses, not unlike that found in the main mass near the optic chiasm. The trochlear nerve was found stretched over the sac on the left side. Both oculo-motor nerves were thin. This was particularly true of the left.

On sectioning of the brain, the entire ventricular system was found to be enormously large and fairly symmetrical. The cyst which was fairly thin walled in its dorsal aspect broke through the floor of the third ventricle, filled the third ventricle and raised a stretched septum pellucidum (fig. 17). The interior of the cyst was filled with numerous collections of crystal-like material and at one point at its ventral aspect, it had a large nodular mass.

*Microscopic observations:* Section of the pituitary, stained with hematoxylin and eosin, showed the latter to be within normal limits, displaying no unusual features except a certain amount of compression. However, directly underlying the hypophysis and intimately at-

tached to it was a zone of wide band of connective tissue which contained islands of embryonal residues, some characteristic of hypophyseal duct remnants. There were long strips of stratified epithelium with a distinct basal layer. In other parts, there were collections of hornified epithelium, some showing deposits of calcium (fig. 18). The free wall of the cyst showed collections of collagenous fibers enveloping islands of hornified epithelium and an occasional foreign body giant cell.

*Comment.* This patient had been under almost constant observation for four years. Early symptoms were those of vegetative disturbances with loss of weight and coincident increase in appetite and thirst. The latter manifestations when added to the focal signs such as ocular muscle disturbances and supranuclear facial paresis, and the x-ray findings (flocculent calcification above the floor of the sella turcica) pointed, of course, to the diagnosis of a suprasellar cyst. This was verified by a craniotomy and histological studies of biopsied material. Recurrent convulsive seizures which simulated idiopathic epilepsy

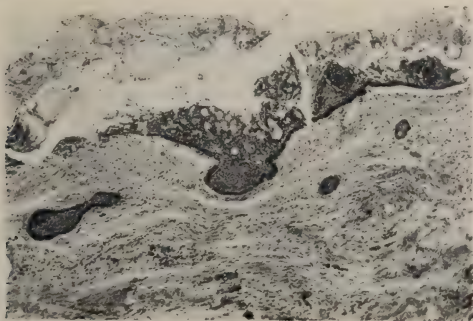


FIG. 18 (Case 5). Section of the cyst wall attached to the pituitary showing hypophyseal duct embryonal residues.

marked the post-operative course. In spite of her three readmissions, further surgical intervention was regarded as hazardous; the post mortem findings justified this decision.

*Case 6. Cystic hypophyseal duct tumor (craniopharyngeoma).* Early symptoms dated back to the age of 12 when he began to manifest signs of vegetative disturbances. Mental alterations preceded his admission to the hospital. There followed polydipsia and polyuria, recurrent frontal headaches accompanied by amblyopia, Jacksonian seizures, and infantilism. Craniotomy disclosed tumor in the region of the optic chiasm and was followed by a rapid decline. A revision of the surgical wound with subtotal removal of the tumor. *Eritus.*

*History:* R. H. (P.M. #10850), a boy aged 15 years, was normal at birth and developed normally until the age of 12 years when he seemed to cease to grow. At that time it was noted that he was rather small for his age and somewhat feminine in appearance. In the subsequent three years he did not increase in height at all, but during the one and a half years before admission to the hospital, he gained approximately 30 pounds. Five months prior to his admission, he began to lose progressively in weight. At the same time he be-

gan to exhibit changes in personality; formerly a bright active student, he became indifferent, dull, seclusive, irritable and subject to increasing somnolence, often sleeping as if in stupor. During that time he became subject to attacks of nausea and projectile vomiting, which increased in frequency, occurring at any time of the day. For the last three to four months, he developed excessive thirst consuming as much as thirty glasses of water a day and voided large quantities of urine. In the last winter he had been unusually sensitive to cold and often had chills at night. During the last four months, he was subject to recurrent frontal headaches associated with dimness of vision. He was treated by injections of endocrine substances. When seen at the Consultation Service of this hospital, it was thought that the patient had an expanding lesion in the suprasellar region affecting both pituitary and tuber cinereum functions. Three months prior to his admission to this hospital, a craniotomy was done at a Jersey City hospital. A neoplasm in the region of the optic chiasm was found. He remained in that hospital for one month in a state of apathy, somnolence and carelessness in habits. He was unable to feed himself. Clonic spasms occurred repeatedly on the right side of his body which was always held rigid. He lost weight rapidly. He voided large quantities of urine and vomited frequently. A visible swelling at the site of his right frontal craniotomy scar developed, and he was brought to this hospital.

*Examination:* The patient, aged 15 years, had the appearance of a boy of 8 to 10 years. He soiled himself frequently. The skull was relatively large with prominent frontal bosses. It exhibited a well healed right frontal craniotomy scar with the bone flap being elevated over its superior posterior aspect. In the region of the anterior inferior burr hole there was a soft, non-pulsating swelling. Secondary sex characters were poorly developed, and there was a eunuchoid type of obesity.

The patient was well oriented. He was responsive at some times, giving quick, intelligent answers and at other times seemed completely out of contact with his environment. He was hypoactive and showed retardation. He stated that he understood commands but often made no effort to execute them. His memory appeared impaired. Paragraphia and perseveration were present. Bilateral papilledema was noted with some temporal pallor. He exhibited purposeless rolling of his head and trembling of his extremities. There were clonic movements of the left arm, and a tendency to bilateral grasp reflexes. The knee jerks were active bilaterally. There was paresis and hypotonicity of all limbs.

*Laboratory data:* The cerebrospinal fluid was clear and yellowish; it contained 266 cells of which 260 were well preserved red blood cells and 6 white blood cells, the latter consisting of 2 polymorphonuclear neutrophils and 4 large monocytes. The initial pressure of cerebrospinal fluid was 130 mm. and the final pressure, 10 mm. The Pandy test was 3 plus. The urine contained 2 plus albumin and granular casts. The blood Wassermann reaction was negative. The blood chemical studies were negative.

*Course:* The diagnosis of a suprasellar expanding lesion was made. The probability that the third ventricle was invaded and the hypothalamic region affected was considered. A right fronto-parietal craniotomy was performed with a subtotal removal of the tumor. Approximately three hours after the operation, the patient's condition became very poor. His temperature rose to 108°F., and the pulse rate was 196 per minute. He died on the same day.

*Surgical specimen:* (#63460). It consisted of many small fragments of tissue, some of which were firm and rubbery in consistency and others of calcareous hardness. Some of the fragments were studded with small yellowish crystalline bodies and showed many hemorrhagic areas. The tissues were floating in a reddish yellow opaque viscid fluid which had been aspirated from the cystic mass found at operation.

Sections of surgically removed tissue displayed the following features: there was a fairly large mass of slightly disorganized brain tissue containing islands of what appeared to be embryonal remnants. The latter were characterized by irregularly walled regions of tissue presenting a free surface lined by pseudo-stratified epithelium underneath which there was a reticulum of mesenchymatous material. Within the latter there were many ring-

like structures containing epithelial cells forming whorls. In other parts similar rings were filled with epithelial cells which had undergone hyalinization. Then there were other rings which were lined by single layered epithelium filled with a homogeneous eosinophilic material. There was a strong possibility that tissue from the main mass of the tumor itself would indicate a more solid character of the neoplastic process. While the diagnosis of craniopharyngeoma was considered, the possibility of an adamantinomatous form of craniopharyngeoma was also borne in mind.

*Necropsy findings. Brain. Gross:* The removal of the brain proved difficult and resulted in laceration of the left temporal lobe. The striking feature was the cyst which rose out of the floor of the third ventricle in the region of the hypophyseal stalk and the discolored walls of which could be seen spreading up the left wall of the ventricle. The cyst seemed to consist of two parts: one, spherical about 2 to 3 cm. in diameter (the wall of which was torn), in the anterior part of the ventricle; the other, non-communicating, about 4 cm. long and  $\frac{1}{2}$  cm. wide, extended obliquely, posteriorly and upward, pointing toward the aqueduct of Sylvius. Hard, yellow, gritty-feeling masses were felt and seen about the basal part of the spherical cyst.

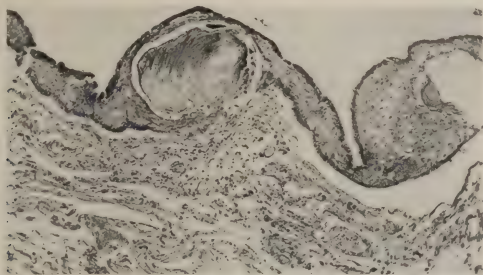


FIG. 19 (Case 6). Section of the cyst showing a layer of stratified squamous epithelium supported by loose connective tissue and containing hornified epithelium inclusions. Hematoxylin and eosin stain.

On sectioning of the brain, a large cyst was found in the region of the interpeduncular space. It measured about 2 cm. in the vertical diameter and about  $2\frac{1}{2}$  cm. in the horizontal diameter. Its upper surface had displaced the thalamus upward, having foreshortened the third ventricle in its vertical plane. The mesial surface of the cyst was firmly attached to adjacent brain tissue and only a narrow portion of its dorsal aspect was found to be free. Near its anterior extremity the anterior pillar of the fornix was found to fuse with the external wall of the cyst.

The *pituitary body*, except for its more fleshy appearance, was grossly normal.

*Microscopic observations:* Section of the cyst wall showed it to consist of a thin layer of stratified squamous epithelium, containing fairly numerous collections of hornified and some keratinized squamous epithelial cells (fig. 19). The epithelial lining overlay a collection of homogenized material which showed throughout breaks, simulating spaces of dissolved cholesterin crystals.

*Comment.* In this instance, infantilism and vegetative disturbances, namely, marked fluctuation in weight, the disintegration of personality, the development of increased intracranial tension accompanied with polydipsia and polyuria, all pointed to the diagnosis of suprasellar cyst. The appearance of unusual



sensitivity to cold may be regarded as another feature of hypothalamic disorder. The development of decerebrate rigidity is a striking manifestation, but is not out of keeping with the location of the expanding lesion leading to disturbances within the midbrain.

*Case 7. Cystic hypophyseal duct tumor (craniopharyngeoma) in a girl aged 16 years. Signs of intracranial involvement appeared at the age of 7 years and ventriculography then disclosed an obstructed third ventricle, but craniotomy failed to disclose the lesion. Decompression led to temporary improvement. Five subsequent admissions. Gradual development of vegetative disturbances, mental deterioration. X-ray revealed calcification above sella. A surgical revision at which part of the cystic tumor was removed. Recovery interrupted a few weeks later by signs of increased intracranial tension. A second revision of operative field and cyst emptied of 60 cc. fluid with large part of the cystic wall removed. Rapid decline and exitus.*

*History:* E. S. (Surg. #82843; 85859), had six admissions to this hospital. When she first entered this hospital on October 30, 1935 she was 7 years of age. She apparently was well until six weeks prior to that admission when she fell while skating and struck the back of her head. She did not lose consciousness, was able to get up and return home without apparent difficulty. The following day on her return from school, she complained of frontal and temporal headaches. She vomited. Headache and vomiting recurred throughout the next two weeks and she was taken to a local hospital. There a subdural hematoma was suspected but various laboratory studies excluded it as a diagnostic possibility. She was then brought to this hospital.

*Examination:* The child appeared to be undernourished. There was marked percussion tenderness throughout the skull and a rather slow pulse. Blood pressure was 102 systolic and 74 diastolic. The pupils were fixed to light and accommodation; they were irregular and unequal, the right larger than the left. The left palpebral fissure was wider than the right. The fundi showed slight pallor. There was a suggestion of a left homonymous hemianopsia. There was some weakness of the left upper extremity and a somewhat unsteady gait. The deep reflexes were absent in the upper extremities and diminished in the lower. There was a Babinski sign on the left side. The child was alert, somewhat overactive and overtalkative. Lumbar puncture yielded fluid at a normal pressure, containing 10 lymphocytes per cu. mm.

*Course:* An expanding lesion was considered and a ventriculography was performed. The latter showed moderate dilatation of both lateral ventricles. The third ventricle failed to fill. Ventriculography was repeated and again the 3rd ventricle did not fill. It was then decided to explore the region in a two stage operation. As a result of the decompression provided by the first stage of the operation, the patient's condition improved so remarkably that the second stage of the procedure was thought unnecessary. The headache disappeared and she no longer vomited. Her conduct improved and there was a gain of weight. She left the hospital on November 27, 1935.

*Second admission:* She returned seven months later on June 14, 1936. It was related that she continued to be in apparently good health until one week before readmission when she fell out of a swing and struck her head against a tree. This was followed by dizziness, drowsiness and projectile vomiting. At the hospital the child was found to be alert and cooperative. The decompression in the right parietal region was bulging but soft. Neurological status was essentially the same at the time of discharge. A lumbar puncture was done and clear fluid was obtained under an initial pressure of 100 mm. of water. During her subsequent days in the hospital, the patient vomited repeatedly; periods of drowsiness alternated with episodes of hyperactivity. Another lumbar puncture revealed xanthochromic fluid with 600 red cells per cu. mm., while a subsequent third lumbar puncture revealed a normal fluid under normal pressure. Throughout her stay in the hospital, she manifested an extraordinary irregularity of the pulse, which ranged from 54 to 128 per



minute. At the end of three weeks, she became more alert, vomiting ceased, restlessness diminished and she was allowed to return home.

*Third admission:* She reentered the hospital at the age of 15, on April 27, 1943. The interval history as depicted by the Follow-Up record showed that the patient did well for a period of seven years. She began to menstruate early at the age of 10. She was free of headache, did not vomit and was free of symptoms until the age of 14 years when she began to display conduct disorder, began to confabulate and show disinclination to do her school work. Following the fall from a chair, eight months prior to her readmission, she developed a persistent incontinence of urine. At this time, she exhibited in addition to her previous signs, bilateral Oppenheim and Chaddock signs. There was a basal metabolic rate of minus 23 per cent. The cerebrospinal fluid was under normal pressure. X-ray examination of the skull disclosed a large amount of calcification above the sella. She improved

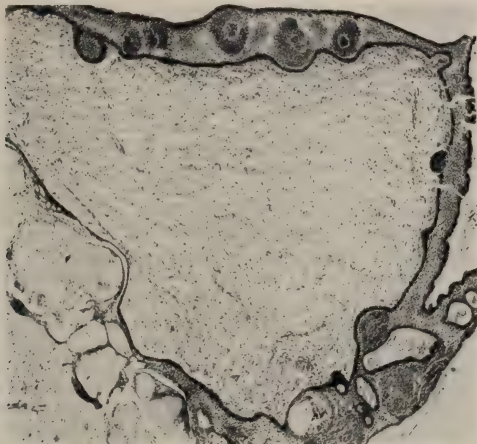


FIG. 20 (Case 7). Section of the surgical specimen revealing typical features of cystic craniopharyngioma (see text). Hematoxylin and eosin stain.

while in the hospital and was allowed to return home at the end of the week. The diagnosis of craniopharyngioma was made at this time.

*Fourth admission:* On May 1943, she reentered the hospital for further study. A pneumoencephalogram showed both lateral ventricles to be enlarged with the left displaced upward and medially and the right displaced somewhat laterally. A large filling defect was seen in the anterior portion of the left lateral ventricle. The findings indicated a suprasellar mass in the midline and slightly to the left. Surgical intervention was considered to be too hazardous.

*Fifth admission:* She reentered the hospital on July 5, 1943 with a bulging decompression and bilateral papilledema. She was subjected to a craniotomy and partial removal of the wall of the craniopharyngioma. Following the operation, there was marked improvement and she left the hospital on August 10, 1943.

*Surgical specimen:* Portion of cyst wall consisted of a mass of tissue globoid in shape, weight  $1\frac{1}{2}$  Gm. It was hard, although slightly elastic and showed a few cartilaginous spots.

Section consisted of a stroma of connective tissue which was covered by fairly wide band

of stratified squamous epithelium. The latter showed typical arrangement of embryonal skin, displaying an early hair follicle formation, collections of hornified epithelium, and in some instances it gave rise to multilobular cyst formation, each one lined by a narrow band of squamous epithelium, the contents of which was a homogenized pink-staining substance (fig. 20).

*Sixth admission:* The patient remained free of symptoms for a few weeks following her return home, and then began to complain of headache, vomiting frequently and displaying personality changes with incontinence of urine. Examination revealed unequal pupils, the right larger than the left, optic atrophy on the right, hyperactive deep reflexes, bilateral Babinski signs, and questionable blurring of the discs on the left. The operative field was revised and the cyst approached through the hemisphere. It was found to be large, containing an estimated 60 cc. of fluid. A great deal of the wall was removed and in the process of the removal, a large arterial trunk was cut. The bleeding was controlled. Following the operation, the patient did not do well. Her condition declined gradually and she died seven weeks after the operation.

*Surgical specimen:* The material consisted of about 15 fragments of tissue having the appearance of a wall of a cyst. The interior was sprinkled with crystal-looking calcium deposits. In a few areas, the wall was thickened and contained a cyst-like structure.

This section consisted of a layer of connective tissue containing large collections of small round cells. Within this connective tissue there were islands of hornified epithelium which were surrounded by bands of stratified squamous epithelium of the embryonal variety. These contained an occasional collection of cells simulating formation of hair follicles.

*Comment.* In this instance the patient was under observation for a period of over nine years. Early symptoms began at the age of seven years. A history of a fall seemed to mark the onset of symptoms. There was loss of consciousness, with no immediate sequelae and it was doubtful whether the injury contributed anything to the clinical picture. Six weeks after her alleged injury, she began to display focalizing signs, most significant among which were irregular, unequal pupils, fixed to light, early primary optic atrophy, and left homonymous hemianopsia. An exploratory craniotomy failed to disclose the lesion and only eight years later when a large amount of calcification above the sella turcica was revealed by x-ray examination was the nature of the tumor recognized. At that time she presented other signs favoring this diagnosis, such as the moderate amount of infantilism, low metabolic rate, and what was described as urinary incontinence. They all pointed to probable hypothalamic involvement. This was verified on her fifth admission by a craniotomy and histological study of biopsied material. Subsequent events were characterized by decline and further removal of the cyst wall and its contents did not alter the final fatal issue.

*Case 8. Cystic hypophyseal duct tumor (craniopharyngeoma) in a woman aged 27 years.* Signs and symptoms began at the age of 20. Amenorrhea, cachexia, loss of axillary and pubic hairs, ocular muscle involvement and signs of increased intracranial tension. Deep x-ray therapy with doubtful temporary improvement. Craniotomy, cystic tumor in proximity of optic chiasm found and emptied of its contents. Convalescence with some improvement interrupted by recurrence of headache, vomiting, somnolence and pain, temperature and pulse dissociation. Signs of meningeal irritation and exitus.

*History:* A. M. (P.M. #8859), a white married woman, aged 25 years at the time of her first admission, was apparently well until the age of 20. At that time she became

amenorrheic. Within the next three years she exhibited an appreciable loss of weight, anorexia and generalized weakness. About the same time she complained of polyuria and parieto-occipital headaches. In another two years she noticed failing vision and turning outward of the left eye. At about the same time, she began to vomit frequently and complained of occasional attacks of vertigo. Within that year she noticed a loss of hair under the axilla and over the pubis.

*Examination:* The patient was of small stature, and had scanty pubic and axillary hair. Her teeth were wide spaced and the external and internal genitalia were recorded as being infantile. She appeared to be anemic and poorly nourished. Blood pressure was 100 systolic and 84 diastolic.

The neurologic findings included the following: bilateral optic atrophy with superimposed papilledema; bitemporal hemianopsia; diminished visual acuity: O.D. 15/20, L.S. 15/50; left internal rectus weakness; unequal pupils, the right larger than the left, both reacting to light; a right central facial asymmetry; an equivocal Babinski sign on the right.

*Laboratory data:* The basal metabolic rate was minus 10. Hemoglobin was 65 per cent, with 3,700,000 red blood cells. White blood count was 6,400 with 55 per cent lymphocytes. The blood Wassermann reaction was negative. X-ray examination of the skull revealed a greatly enlarged sella turcica, erosion of the posterior clinoids, depression in the sphenoid sinus and suggested irregular calcification in the suprasellar region.

*Course:* The diagnosis of a pituitary neoplasm with probable extension into the suprasellar region was made. Operation was considered inadvisable because of the poor condition of the patient. She was given x-ray therapy which resulted in some improvement in the visual fields. After a stay of eight days, she left the hospital.

The x-ray therapy was continued and completed after nine exposures. She showed further improvement, gaining 15 pounds. Headaches and vomiting subsided and polydipsia and polyuria diminished. There appeared a slight increase in the pubic hair and there was one brief episode of vaginal bleeding. She also showed improvement in her mental faculties.

The improvement was only temporary, a decline in her condition reappeared. The blurring of vision reappeared in both eyes, especially in the left, and she was readmitted to the hospital in April 1933. At this time visual acuity had depreciated markedly, O.D. 20/200; O.S. 6/200. She was then subjected to a transfrontal craniotomy on April 10, 1933. A cystic tumor was found in the proximity of the optic chiasm. Its capsule was partially excised and its contents emptied.

Following the operation and for a period of 3 weeks, the patient ran an unusual type of temperature which was considered hypothalamic in origin. There was dissociation between the temperature and the pulse rate. Then moderate improvement set in. Some vision was regained. She also gained some weight. Her basal metabolic rate dropped from minus 19 to minus 29. Her anemia became more marked. Gastric analysis showed complete achlorhydria. In the course of the next few weeks the blood picture improved and she was discharged on May 30, 1933. But soon after her discharge from the hospital, severe headaches, frequent vomiting and impaired vision recurred. Her mental state varied between somnolence and delirium. She was readmitted on June 9, 1933 and then found to be disoriented, and somewhat lethargic. She revealed some neck rigidity and bilateral Kernig signs. The right pupil was fixed to direct stimulation but reacted consensually. She was almost totally blind. Slight ptosis of the right eyelid and right internal rectus paralysis were present. She lost completely the sense of smell and showed a slight lower left facial weakness and bilateral Babinski sign.

*Laboratory data:* Lumbar puncture revealed a somewhat hazy cerebrospinal fluid under increased pressure with about 200 cells per cu. mm. of which 64 per cent were polymorphonuclear lymphocytes and 34 per cent were monocytes. On repeated lumbar punctures, the cell count became higher. At no time were organisms found by culture or smear.

It was thought that an effusion of the contents of the pituitary cyst had caused meningeal

irritation. Her condition declined gradually and she continued to run a febrile course. It was found inadvisable to explore her and she died 6½ weeks after her final admission.

*Necropsy findings. Brain. Gross:* The brain was of normal size and slightly injected. At the base of the brain in the region of the pituitary there was an organized discolored mass in which were involved the optic chiasm and nerves. It was not possible to distinguish individual structures. At the postero-medial angle at the base of the left frontal lobe there was a small cystic swelling from which a brownish cloudy fluid could be expressed. The pituitary fossa of the sphenoid bone appeared clear, and did not contain any recognizable *pituitary body*. Covering the base of the brain stem and the inferior surface of the cerebellar hemispheres was a yellowish fibrinous exudate. Smears from this exudate showed degenerated polymorphonuclears and mononuclears in about equal numbers and a small number of gram positive cocci singly, in pairs and in clumps, many of them intracellular.

On sectioning of the brain, a circular area in the left hemisphere in the region of the inferior portion of the frontal lobe on level of the temporal pole occupying the subcortical

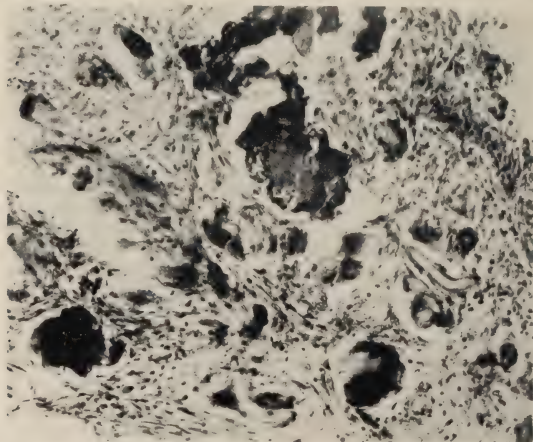


FIG. 21 (Case 8). Section of the wall of the cyst showing collections of hornified and calcified epithelium with scattered foreign body giant cells. Hematoxylin and eosin stain.

region was well demarcated from the adjacent brain substance by a thin capsule and enclosed yellowish gray material. On its ventral aspect, it was surrounded by a crescentic zone of a similar character. Tracing this area backwards it assumed the character of an area of softened tissue, surrounded by a hemorrhagic zone. It extended backward as far as the pituitary region. It was still limited to the left hemisphere. In the region of the pituitary and tuber cinereum there was an irregular large indurated mass. It was linked to the right hemisphere by an area of softened tissue. The ventricular system was distended. The right lateral ventricle was larger than the left in the region of the anterior horn and bodies. The descending horns were within normal limits, but the posterior horns were somewhat larger, the right being larger than the left. The circular zone described had the appearance of an abscess, which had not reached complete suppuration.

*Microscopic observations:* Sections of the mass in the interpeduncular space stained with hematoxylin and eosin revealed a collection of epithelial cells with acinar formation.



Within this region there were numerous calcified bodies, hyalinized epithelial cells, multinucleated foreign body giant cells (fig. 21). Adjacent to this area there were numerous collections of heavily pigment laden phagocytes, inflammatory scar tissue and giant cells. These surrounded large irregular hyalinized bodies.

*Comment.* This case of a woman aged 27 years, aside from the fact that she began to manifest evidences of endocrine and hypothalamic disturbances, such as amenorrhea, associated with polydipsia and polyuria, yields no features of unusual character except perhaps for the dissociation of pulse and temperature curve.

*Case 9. Cystic hypophyseal duct tumor (craniopharyngeoma) in a woman aged 50 years.* Onset  $1\frac{1}{2}$  years prior to admission with diplopia, followed by excessive fatigability; severe headache and vomiting; focal signs, suggesting chronic basilar meningitis. X-ray revealed erosion of dorsum sellae. Anti-luetic treatment; deep x-ray therapy followed by improvement. Convalescence interrupted by headaches, dysphagia, dysphonia and an unsteady gait. Craniotomy interrupted by poor condition of the patient. Exitus 12 hours later.

*History:* E. S. (P.M. X398), a woman, aged 50 years, was apparently well until  $1\frac{1}{2}$  years prior to her admission to the hospital. At that time, following a cold, she suddenly developed double vision. Shortly thereafter, it was noticed that her eyes turned inward. One year later she began to complain of excessive fatigability, and her ocular disturbances became more pronounced. During the two months before admission, she began to have severe headaches which were accompanied by vomiting and regurgitation of food. At the same time her left upper eyelid began to droop and finally the entire left palpebral fissure was closed. In the course of the last two weeks, the right upper eyelid began to droop. She then entered the hospital.

*Examination:* The significant neurological findings included bilateral paralysis of the third nerve and paralysis of the right sixth nerve.

*Course:* The first clinical impression was that of chronic basilar meningitis. Although the cerebrospinal fluid and blood Wassermann reactions were negative and there was no abnormal number of cells in the cerebrospinal fluid, a luetic character of the meningitis was considered. X-ray examination of the skull, however, showed a marked erosion of the dorsum sellae and the posterior clinoid processes. An area of calcification was noted in the left frontal region involving the inner plate. The patient, nevertheless, was given a course of anti-luetic treatment which seemed to bring about some improvement. Both visual fields showed slight concentric constriction; there was no absolute scotoma but some confusion of blue and green in both eyes. In view of the x-ray demonstration of sellar destruction and the probable existence of a pituitary tumor, she was given a course of deep x-ray therapy. She responded with further improvement so that at the time she left the hospital, there was only slight restriction of function of the intrinsic and extrinsic eye muscles, and the pupils reacted to light and on convergence. There was less paresis of the eyelids.

She returned to the hospital two months later because of the development of headaches, difficulty in swallowing, impairment of voice, loss of weight and a tendency to fall backward. At this time she exhibited a complete third nerve palsy on the left side and a right central facial weakness, unsteady gait and a nasal speech. An encephalography was carried out and a moderate dilatation of the ventricles was found. The posterior end of the third ventricle was not visualized and there was some displacement posteriorly of the aqueduct and the fourth ventricle. An exploratory operation was carried out and a tumor was found in the interpeduncular region. The operation had to be interrupted because of the poor condition of the patient. She died 12 hours later.

*Necropsy findings. Brain. Gross:* A cystic tumor was found in the region of the interpeduncular space (fig. 22). It was intimately adherent to the underlying basilar portion of the occipital bone. The overlying structures were free. The third nerve on the left side was displaced to the left. The anterior end of the cyst protruded forward beyond the



interpeduncular space underneath the temporal pole on the left side. The cyst was filled with brownish red material, and collapsed on removal. It had a bluish capsule which showed in several areas nodular protuberances. The sella turcica was deep, and the *pituitary body* was small and apparently separate from the tumor cyst.

*Microscopic observations:* Section of the wall of the cyst, stained with hematoxylin and eosin, displayed small collections of stratified squamous epithelium. There were also fairly large fragments of bone formation surrounded by large masses of cells characterized by a central pyknotic nucleus and a large mass of granular cytoplasm. Within these cell masses

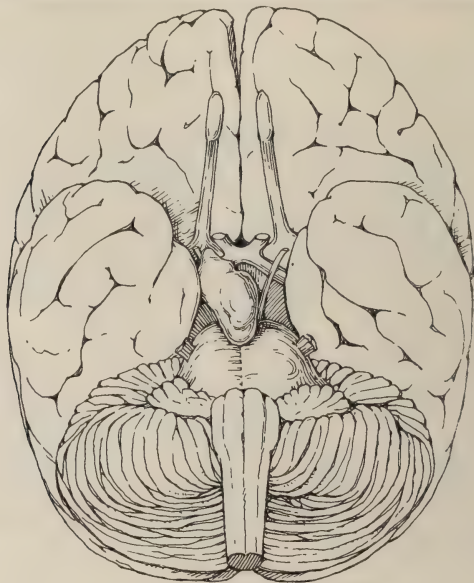


FIG. 22 (Case 9). Drawing reconstructing the appearance and location of the cyst there were small islands of bone (fig. 23). In one part of the cyst wall there were glandular structures simulating those of the mature massa intermedia.

*Comment.* Of interest in this case is the presence of a craniopharyngeal cyst in a woman aged 50 years. The early signs and symptoms simulated those of a chronic basilar meningitis and she was treated accordingly for a while in spite of the disclosure of erosion of dorsum sellae.

*Case 10. Solid hypophyseal duct tumor (adamantinoma) in a boy aged 10 years. One year before admission, bilateral optic atrophy. Shortly before admission to the hospital, sudden onset of headache and vomiting. Temporary improvement followed by lethargy, head-*

ache and vomiting. In addition to pallor of both discs, limitation of eye movements to the left, diminution of visual acuity, right homonymous hemianopsia, there were focal signs with evidence of meningeal irritation. Episodes of decerebrate rigidity. Papilledema. Generalized convulsion. Rapid decline, exitus.

*History:* P. Z. (P.M. #7104), a boy, aged 10 years, was said to have been well until two months before he was admitted to The Mount Sinai Hospital (February 1, 1930), with the exception that an ophthalmologist several years previously had observed changes in the patient's discs which he considered to be an optic atrophy. His illness began abruptly with a sudden onset of headaches followed shortly by vomiting. A physician who examined the child regarded sinusitis as the cause of the symptoms and prescribed steam inhalation. The following morning the patient was apparently well again and free from symptoms. Shortly thereafter, however, he was found to be somewhat lethargic, irritable and occasionally complained of headaches which were followed by vomiting. This state continued until

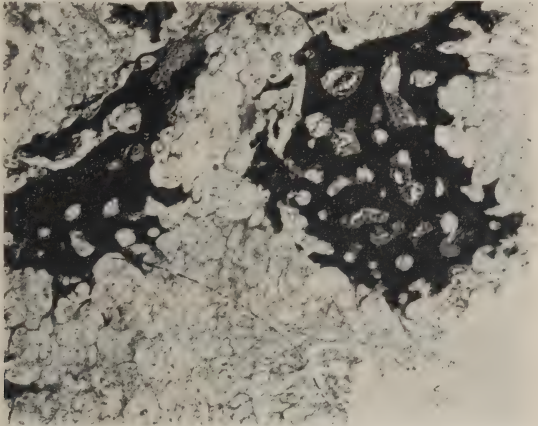


FIG. 23 (Case 9). Section of the cyst wall showing the peculiar cell groups (see text) and the islands of bone tissue. Hematoxylin and eosin stain.

one week before he entered the hospital when the frontal headaches became more intense and he complained of difficulty in breathing. He vomited several times and passed through episodes of drowsiness.

*Examination:* The patient was a rather well developed boy who appeared quite drowsy. His fundi showed a gray pallor of both discs, and there appeared to be some limitations of the movements of the eyes to the left. There was diminution of visual acuity and a right homonymous hemianopsia. There was a right central facial paresis with some deviation of the tongue to the right. The right arm and leg were weak, the deep reflexes on that side being more active than on the left side. The right upper abdominal reflex was the only one obtained. There was a right Babinski sign. His neck was rigid, with a moderate bilateral Kernig sign. His gait was staggering. There was a marked tremor of both hands with aimless spontaneous movements of all the extremities.

*Laboratory data:* A lumbar puncture yielded apparently clear fluid which on study re-

vealed 480 cells with 95 per cent monocytes per cu. mm. A subsequent lumbar puncture showed similar fluid with a cell count of 70, of which 90 per cent were monocytes. X-ray examination of the chest was negative.

*Course:* On the day of admission, the patient passed through an attack of decerebrate rigidity, assuming a position of extreme opisthotonos with all the extremities rigidly extended and the eyes rolled upward. While the right upper and lower extremities were rigid in extension, the right forearm tended toward pronation. This episode, during which the patient lost consciousness, lasted about five minutes, and left, as a residual finding, a marked spasticity on the right side of the body. The patient passed through several similar attacks on that day. The following day, the unilateral rigidity of the body disappeared and the patient returned to his previous state of alertness and relative comfort. In view of these attacks, and the pallor of the discs, an expanding lesion in the left hemisphere was suspected. With the advance of time, he seemed to regain some power in the right extremities and the hemianopsia had also seemed to disappear. However, the mental state of the patient was punctuated by episodes of drowsiness and was marked by impairment of memory. The Kernig signs became more marked, and the deep reflexes were no longer obtainable. At times a bilateral ptosis of the eye lids was noted. The possibility of a meningeal invasion, either inflammatory or sarcomatous in character, was considered. However, papilledema appeared, and it was decided to aspirate the ventricles (February 26, 1930). There was found a markedly dilated ventricle on the left side. Following this procedure, the patient remained comatose, developed Cheyne-Stokes breathing and again exhibited episodes of decerebrate rigidity. Several days later he had a generalized convulsion and for a brief period he seemed to come out of the coma. Improvement was only temporary, and he ceased on March 3rd.

*Necropsy findings. Brain. Gross:* On reflecting the dura, the brain was seen to be voluminous and unusually soft and showed evidence of intracranial pressure. On lifting up the frontal lobes some difficulty was encountered due to an adherent tumor mass in the region of the sella turcica. This mass lay partly on the floor of the sella turcica which was greatly widened, while the upper part of the tumor occupied the interpeduncular space and was partly imbedded in the brain substance (fig. 24). The tumor measured about 6 cm. in its longitudinal diameter and 3 cm. in its transverse diameter. It was rather firm although in some places there was cystic formation. It was pinkish in color and was covered by a rather firm capsule. The optic nerves were very much flattened and compressed by the lateral parts of this tumor mass. The interpeduncular cistern posterior to the tumor was tremendously dilated with some fluid of dark opaque character. The pituitary gland could not be found after the extirpation of the tumor and was assumed to form part of the tumor mass.

On sectioning of the brain, in a median sagittal plane, a large tumor was found, occupying the entire third ventricle (fig. 25). The tumor mass was well encapsulated, shelled out easily from the ventricular cavity and on sectioning, showed a granular appearance, a rather glistening surface, an occasional small cyst and a suggestion of alveolar arrangement. At the anterior part on its undersurface, a small nodule, measuring about 3 mm. in its long diameter, wedge-shaped and attached to the capsule of the main tumor, was found and since no pituitary gland was found in the sella turcica, it is probable that the small mass was all that was left of the *pituitary body*. The lateral ventricles were symmetrically enlarged.

*Microscopic observations:* The tumor tissue showed three different histologic structures. In parts of the tumor, particularly those which contained small cysts, there were collections of hornified and calcified squamous epithelium, supported by a mass of connective tissue which showed on the surface a thin epithelial lining (fig. 26a). In another part of the tumor, large acini were lined by low cuboidal epithelium (fig. 26b). Some of the acini were filled with colloidal material. This part of the tumor bore strong resemblance to the mature pars intermedia, while in other parts of the tumor, solid buds consisting mainly of stellate cells were lined by tall cuboidal cells which resembled ameloblasts (fig. 27). This type of structure was dominant throughout the tumor.

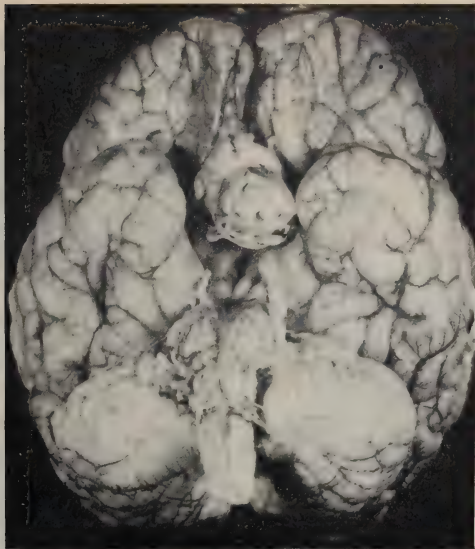


FIG. 24 (Case 10). The base of the brain showing the tumor in the interpeduncular space.

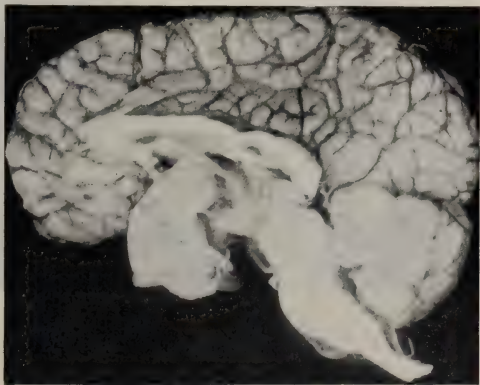


FIG. 25 (Case 10). The median sagittal section of the brain demonstrating the solid character of the interpeduncular tumor.

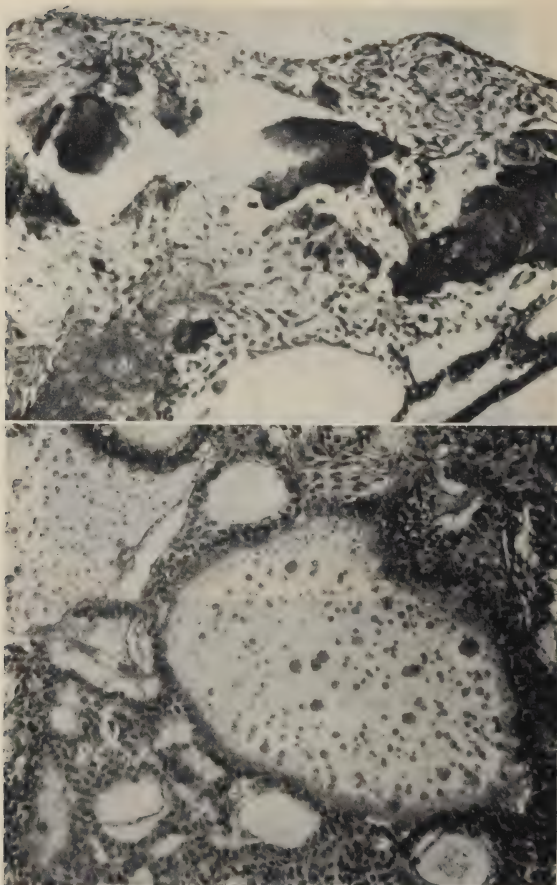


FIG. 26a (Upper) (Case 10). Section of the tumor showing the collections of hornified and calcified epithelium. Hematoxylin and eosin stain.

FIG. 26b (Lower) (Case 10). Section of the tumor displaying structures simulating pars intermedia. Hematoxylin and eosin stain.

*Comment.* Here is the first instance of the second group of our cases in which the tumor is solid and the histologic make-up duplicates the structures derived



from primordia in the embryonal oral cavity. Associated with this, there are also structures which are characteristic of the residua of the hypophyseal duct and some simulating the more mature pars intermedia of the hypophysis. This case manifested evidence of more acute onset and more rapid evolution of the clinical course. The nature of the tumor obviously precluded successful surgical intervention.

*Case 11. Solid hypophyseal duct tumor (adamantinoma) in a man aged 21 years. History of head injury a year earlier, followed by headaches, increasing in severity and frequency. Generalized convulsions, bilateral papilledema, focal signs. Exploratory craniotomy with negative findings. Advancing papilledema; recurrence of headaches; stupor; ocular muscle involvement; pupillary disturbances and signs of meningeal irritation. Exitus.*

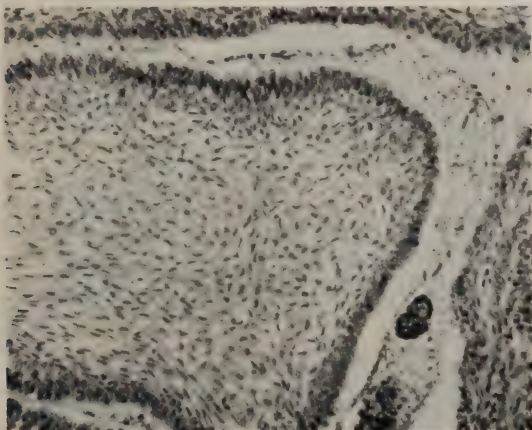


FIG. 27 (Case 10). Section of the tumor showing a layer of ameloblasts overlying a dense mass of stellate cells. Hematoxylin and eosin stain.

*History:* J. R. (P.M. #4664), a man aged 21 years, was admitted to the hospital on June 7, 1923. One year before admission, he was kicked on the head by a horse with no immediate symptoms referable to that injury. Two months later, he began to complain of severe headaches in the frontal region; they were intermittent in occurrence, usually lasting two or three days, then disappearing for an indefinite period. In the course of the last six months, they had increased markedly, both in severity and in the frequency of their occurrence. Five weeks before his admission to the hospital, he was said to have had a generalized convulsion. The patient felt that his memory had been growing appreciably poorer during the last few months of his illness.

*Examination:* The patient exhibited a pathological geniality, with constant smiling and silly, over-emotional behavior. The pupils were equal and regular and reacted to light and on convergence. There was slight horizontal nystagmus, especially on looking to the left. He had bilateral papilledema, one diopter elevation on the right,  $2\frac{1}{2}$  diopeters on the left. There was a left lower facial weakness. Hyperalgesia of the entire left side of the body,

including the face, was present. The deep tendon reflexes were all present and equal; the abdominal reflexes were active. There was a suggestive left Babinski sign.

*Laboratory data:* Urine, blood cytology and blood Wassermann reaction were negative. X-ray examination of the skull was negative.

*Course:* At the end of the first week in the hospital, the left central facial paresis had become much more pronounced and it was noted that the left patellar and suprapatellar reflexes became more lively than the right. The Babinski sign on the left was now definite. His visual fields showed bilateral, generally and symmetrically contracted fields. Barány tests were negative. On June 15, 1923 an exploratory craniotomy was performed. No abnormalities were noted at this time. The patient made a satisfactory recovery from his operation and remained at the hospital until July 17. During this post-operative period the papilledema advanced and showed  $2\frac{1}{2}$  diopters elevation on the right and 3 diopters on the left. He left the hospital for a few months.

In December 1923, he was again operated on. There is no data available as to what was found at that time. At any rate, he was quite well until April 1924, when he again began to complain of severe headaches. On April 25 he had a severe convulsion and lost consciousness. He reentered this hospital the following day.

On readmission he was found to be in deep coma. His eyes were deviated to the right. The pupils were fixed to light. The fundi showed bilateral longstanding papilledema with atrophy. His limbs were all in extension, and the left arm appeared especially weak while the right arm displayed marked purposeless movements. All the deep reflexes were active, except the right Achilles jerk which could not be elicited. The superficial reflexes were absent. There were bilateral Hoffman and Babinski signs.

The patient's condition declined rapidly and he died on the second day in the hospital.

*Necropsy findings. Brain. Gross:* The brain showed evidence of intracranial pressure. There was marked softening in the region of the posterior half of the right frontal lobe, of the adjacent portion of the temporal, and of a narrow zone of the parietal lobe. The base of the brain was markedly distended by accumulations of spinal fluid. In the region of the interpeduncular space there was found a marked elevation (fig. 28) in the floor of the third ventricle in the region of the tuber cinereum, the mammillary bodies having lost their identity. The infundibular duct was markedly distended, passing into a cystic dilatation which replaced the *pituitary body*. The diaphragm of the sella turcica was extremely thin and beneath it was a distended sac measuring about  $1\frac{1}{2}$  cm. in diameter and filled with yellowish, cheesy, granular material. This was all that was left of the pituitary body.

On sectioning of the brain, in a sagittal plane the interpeduncular mass was found to be solid and completely obliterating the third ventricle (fig. 29).

*Microscopic observations:* Section through a characteristic part of the tumor showed a rich stroma of connective tissue enclosing large islands of solid epithelial masses. The latter showed at the periphery a dense layer of columnar cells which bore a strong resemblance to ameloblasts (fig. 30). Within the core of this layer, there were seen epithelial cells forming a syncytium interrupted here and there by stellate cells. In another field, the ameloblasts covered a layer of syncytial cells which in turn overlay a layer of stellate cells surrounding a dense collection of cells suggesting pulp cells.

*Comment.* From the point of view of its histological structure, this tumor is strikingly similar to that in Case 10. Here the adamantinomatous features are more or less uniform throughout the tumor showing none of the characteristics of the cystic hypophyseal duct neoplasm.

*Case 12. Solid hypophyseal duct tumor (craniopharyngeoma) in a woman aged 33 years. Amenorrhea three years earlier. Six months before admission, polydipsia and polyuria followed by headaches, vomiting, dizziness, anosmia, impairment of vision, generalized weakness and bilateral papilledema with retinal hemorrhages. Ventriculography disclosed internal hydrocephalus, obstructing the third and fourth ventricles. Craniotomy, negative findings. Gradual decline, exitus.*

*History:* A. R. (Adm. #460376), a Porto Rican housewife, 33 years of age, entered the hospital on July 26, 1940. Six years earlier she passed through a normal pregnancy and

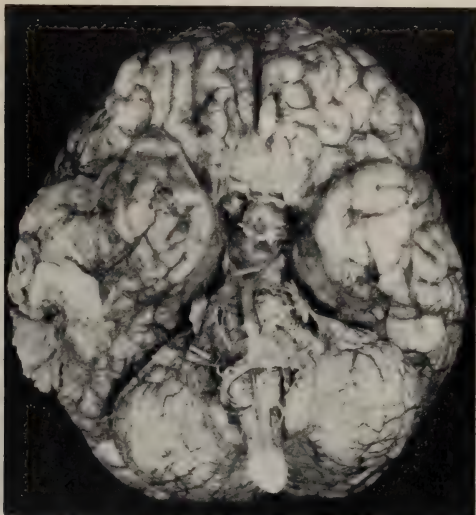


FIG. 28 (Case 11). The base of the brain showing the tumor in the interpeduncular space.

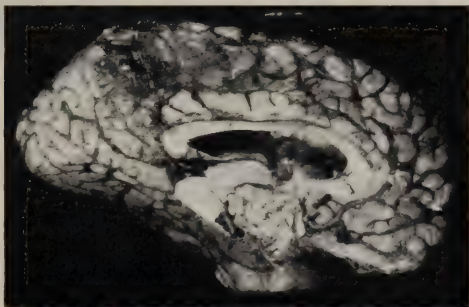


FIG. 29 (Case 11). Median sagittal section of the brain showing the solid interpeduncular mass.

delivery, but shortly thereafter became subject to persistent vaginal bleeding. A laparotomy was performed after which her periods were regular and normal for about 3 years until she again became pregnant. A dilatation and curettage was performed to terminate the

pregnancy. This was followed by an abrupt onset of complete amenorrhea and a moderate gain in weight, from 110 to 119 pounds in the course of the following year. Six months before admission, rather suddenly, she began to experience an increase in thirst and drank copious quantities of water, so that her daily fluid intake averaged at least 14 glasses. At the same time, she developed polyuria and had to get up 7 to 8 times the night to void. One month prior to admission, she began to have headaches, most marked in the frontal and occipital regions, most severe in the mornings and exacerbated by movement. Two weeks later, she began to have attacks of vomiting, occurring when the headache was severe; they were accompanied by nausea, dizziness and epigastric pain. At about this time, she felt feverish, had a bitter taste in her mouth, and could not detect odors as well as previously. Her vision was noticeably impaired. For several weeks prior to admission, she complained of feeling weak and would require progressively longer periods of rest each day.

*Examination:* The patient was a well developed, moderately obese woman. She complained of a severe headache. Heart and lungs were normal, and blood pressure was 104

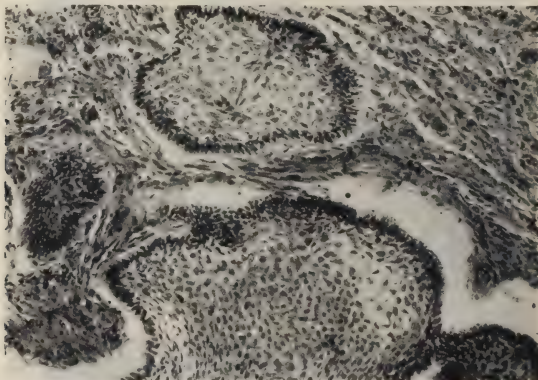


FIG. 30 (Case 11). Section of the tumor mass showing typical ameloblasts lining the solid buds of cellular aggregations, many of which are of the stellate variety. Hematoxylin and eosin stain.

systolic and 60 diastolic. She seemed somewhat depressed, somnolent and slightly irritable.

Neurological examination disclosed only bilateral papilledema more marked on the right with hemorrhages in both discs. There was no impairment of vision, and the visual fields were intact.

*Laboratory data:* A blood count on admission was within normal limits. Urinalysis was negative. The blood Wassermann reaction was negative. The cerebrospinal fluid was clear, under normal pressure, contained no cells, gave negative Pandy, colloidal gold curve and Wassermann reaction. The total protein was 34 mg. per cent. The Janney glucose tolerance test was normal, and there was no glycosuria produced by the test. Basal metabolic rate was 17 per cent. X-ray studies of the skull and chest were negative.

*Course:* On August 6, 1940, ventriculography was performed, revealing marked symmetrical dilatation of the lateral ventricles, while the third and fourth ventricles were not visualized. Shortly thereafter a right fronto-parietal craniotomy was performed on the same date. The third ventricle was exposed but no tumor was found. Sections of the cere-



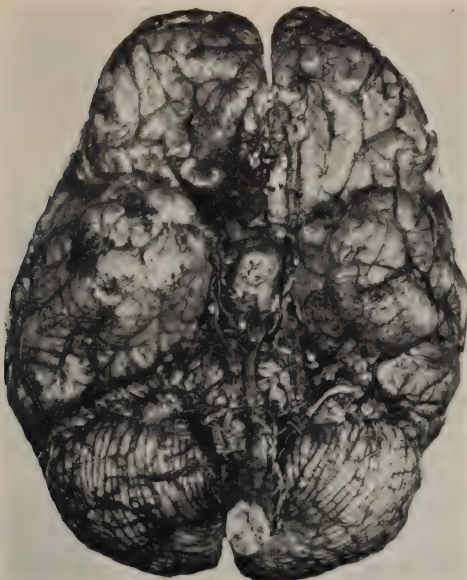


FIG. 31a (Case 12). The base of the brain showing interpeduncular location of the tumor.

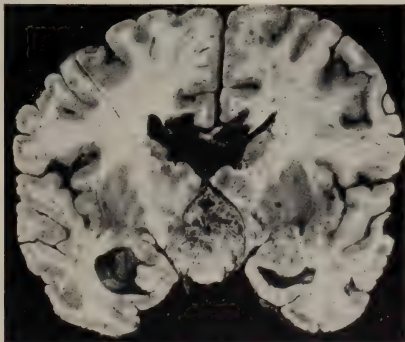


FIG. 31b (Case 12). Coronal section of the brain, showing the location, appearance and consistency of the tumor invading the third ventricle.



bral cortex of the right hemisphere removed at time of operation were reported as not revealing any significant pathological alterations. Post-operatively, the patient became drowsy, her temperature rose, she developed paresis of the left arm and leg, and became incontinent. Two days after the operation, the temperature was 104°F. and she lapsed into coma, with complete paresis of her left arm and leg. An emergency reexploration was performed. A slight extra-dural clot was found. The right frontal lobe was retracted and the right optic nerve exposed, but again no neoplasm was seen. After this procedure, the patient remained in deep coma, and a lumbar puncture yielded xanthochromic cerebrospinal fluid under increased pressure. Despite supportive therapy, coma and hyperthermia persisted and the patient died on the second day after the operation.

*Necropsy findings. Brain. Gross:* An extradural clot was found adherent to the bone flap. Upon removing the brain, which weighed 1300 Gm., and reflecting the dura, considerable clotted blood was found in the superior and posterofrontal regions on the dorsolateral aspect of the right hemisphere. Here also there was seen the operative defect in the cortex which extended ventrally for some distance in the neighborhood of the posterior end of the fissure of Sylvius. The remainder of the brain and its leptomeninges appeared normal in appearance and consistency except at the base of the brain. Here, a tumor was present in the interpeduncular region, which it occupied, completely displacing the optic chiasm anteriorly (fig. 31), and involving all the structures in the floor of the third ventricle. The mammillary bodies were not visible and were apparently incorporated in the tumor. The tumor had a fairly smooth outline and a yellowish color. On palpation it was soft and gave the impression of being cystic, though firmer parts could be made out. The hypophyseal stalk seemed much larger than normal and had a yellow cystic appearance also. The sella turcica was enlarged and its walls were very much thinned, especially in the posterior portion.

The pituitary seemed larger than normal and was yellow in color and of soft cystic consistency.

On sectioning of the brain, the tumor was found to fill completely the third ventricle. The tumor seemed to be adherent to the floor and also part of the walls of the third ventricle, although it could be detached from the upper part of the walls and the roof of the ventricle where it gave the impression of being encapsulated. The tumor was solid in consistency and presented a pearly granular surface with a few small cystic areas filled with grayish gelatinous material.

*Microscopic observations:* Sections of the tumor stained with hematoxylin and eosin and by the Weil and Nissl methods showed it to consist of irregularly branching strands and sheets of closely packed cells supported by a delicate connective tissue stroma. The cells were epithelial in appearance and had large, oval and clearly defined dark-staining nuclei. The outline of the clear staining cytoplasm of these cells was poorly defined except for the periphery of the cellular strands and sheets where they formed a regular row of uniformly sized cells, rectangular in outline (fig. 32a). The cells frequently showed papillary and acinar formations. The centrally placed cells often had a stellate shape giving rise to delicate processes assuming the appearance of cells in mesenchymal tissue; then again they appeared to be rounded; their cytoplasm contained round globules, their nuclei were darkly stained and eccentrically placed.

Small blood sinuses and delicate connective tissue fibers were also seen in the center of the less densely packed cellular aggregations and the connective tissue surrounding these aggregations also had thin, scant fibers and blood sinuses.

Scattered throughout the center of the epithelial cell masses were found small collections of cells which were quite different in appearance. They consisted of closely packed, somewhat flattened, oval or round cells with clear pale pink cytoplasm whose nuclei were either faintly outlined or entirely absent (fig. 32b). The cytoplasm of these cells appeared keratinized and they apparently represented collections of degenerated squamous epithelial cells.

The brain tissue adjacent to the tumor showed an increased number of glial elements,

which together with the neighboring nerve cells, frequently showed advanced degenerative changes. Small collections of tumor cells infiltrated the adjacent brain tissue.

Silver stains revealed the argyrophilic nature of the connective tissue both within and outside of tumor cells.

Sections of the pituitary body revealed the latter to be markedly compressed by tumor tissue, from which it was clearly demarcated. The normal acinar arrangement of the pituitary cells was replaced by flattened ribbon bands of otherwise normal cells. The eosinophile, basophile and chromophobe cells were all present in relatively normal proportions.

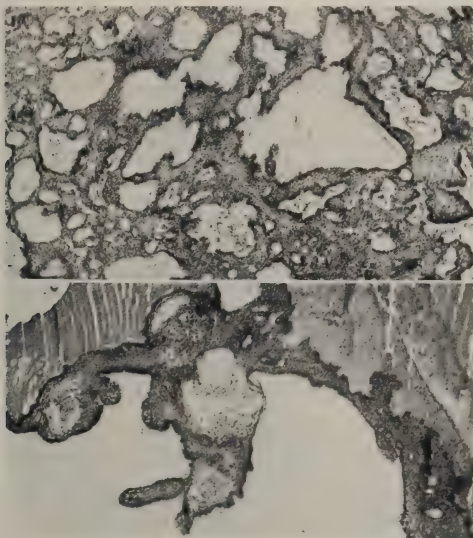


FIG. 32a (Upper) (Case 12). Section of the tumor displaying anastomosing bands of stratified epithelium enclosing space containing hyalinized material.

FIG. 32b (Lower) (Case 12). Section of the tumor showing squamous epithelial lining, with hornified cell enclosures.

*Comment.* In this instance the histological character of the tumor duplicated that noted in the previous two cases (Cases 10 and 11). An added feature is the structure simulating that of the mature pars intermedia with numerous epithelial pearls punctuating various points of the tumor. Histologically, the tumor, despite its solid character, is structurally closer to the hypophyseal duct neoplasm of the craniopharyngeoma variety.

*Case 13.* Solid hypophyseal duct tumor (craniopharyngeoma) in a man aged 42 years. Onset with dimness of vision, headache, polydipsia and polyuria. Loss of libido, loss of aril-

*lary hair. Bitemporal hemianopsia and other focal signs. Craniotomy, rapid decline and exitus.*

*History:* A. W. (P.M. #12129), a man aged 42 years, was apparently well until two years before entering the hospital, when he developed progressive dimness of vision, episodes of moderately severe frontal headache, polydipsia and polyuria, loss of libido, and decrease of axillary hair. Examination at that time revealed bilateral symmetrical temporal field defects. He was given a series of intramuscular injections of unknown nature during the next six weeks, and his symptoms seemed to diappear but the libido did not return.

Two months before entering the hospital, following a tooth extraction, the patient developed severe bifrontal headache aggravated by coughing and straining. During these episodes of headache he was unable to see in the temporal fields bilaterally but overnight this defect would disappear. During the same period, he noticed that his visual acuity was failing gradually.

*Examination:* The patient had mild acromegalic features with large hands. His beard, his axillary, pubic and chest hair were scanty. His breasts were rather prominent. The pupils reacted well to light and on convergence. Visual acuity was 20/70 in the right eye and 20/50 in the left. Ophthalmoscopic examination revealed some pallor of the discs, slightly more marked on the left, and indistinctness of the nasal disc margins. There were bitemporal field defects consisting of multiple paracentral scotomata in the lower temporal quadrants, a right centrally located temporal scotoma, islands of micropsia and teleopsia in both temporal fields (most pronounced in the inferior temporal quadrants), and bitemporal hemianopsia for color (most pronounced in the lower quadrants). Muscle power, reflexes, sensation, coordination, gait and station were within normal limits. The mental status revealed no apparent changes. The blood pressure was 128 systolic and 86 diastolic.

*Laboratory data:* Urine, blood cytology, blood chemistry, and blood Wassermann reaction were all negative. The glucose tolerance test revealed a "flat curve." The basal metabolic rate was minus 6 per cent. Electroencephalography was reported as showing no focal signs, but a diffuse and symmetrical delta activity. Lumbar puncture revealed the cerebrospinal fluid to be under an initial pressure of 130 mm. of water, with normal dynamics, a cell count of 8 lymphocytes per cu. mm., a 4 plus Pandy reaction and protein of 214 mg. per cent; the colloidal gold and Wassermann reactions were negative. X-ray examination of the skull was negative.

*Course:* The diagnosis was tumor in the region of the hypothalamus, probably a craniopharyngeoma. One week after admission a pneumoencephalography was performed. It revealed markedly dilated ventricles with absence of filling of the anterior part of the third ventricle. The patient's fundi showed progressive increase in blurring. After he had recovered from the effects of the pneumoencephalogram, a right frontal craniotomy was performed, on the fifteenth hospital day. On retracting the right frontal lobe the optic nerves appeared displaced anteriorly and laterally by a mass underlying but not attached to the chiasm. On introducing a fine needle into the lesion 3 cc. of clear fluid were aspirated. Aspiration was then attempted from the portion of the lesion lying to the left of the midline; this was followed by profuse arterial bleeding which was controlled with difficulty. It was then noted that the right cerebral hemisphere had become swollen and tense, as though hemorrhage had occurred into the right lateral ventricle. The bone flap was then replaced and a moderate size decompression was left. Following the operation the patient was alternately somnolent, euphoric, facetious and disoriented. Two days after the operation a lumbar puncture revealed bloody cerebrospinal fluid under a pressure of 380 mm. of water; on removal of 50 cc. of fluid the pressure dropped to 70 mm. of water. Subsequent lumbar punctures showed gradual decrease in the amount of blood present; the fluid became xanthochromic two weeks following the operation.

The patient ran an irregular fever with peaks of 102 and 103°F. for ten days after the operation. Although the cause for this fever was obscure, sulfathiazole was given. This was discontinued after the temperature fell to about 99°F. A few days later the temperature rose again to 104°F. A week after the second rise in temperature, some evidence of pneumonia in the right base was noted.

The patient became progressively more stuporous, developed twitching of the hands and lower facial muscles on both sides, and later exhibited a bilateral grasp reflex. He died at the end of the sixth week in the hospital.

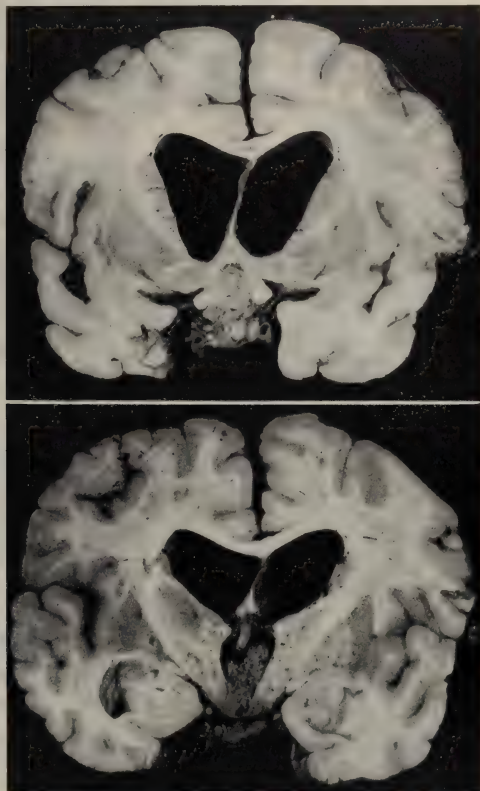


FIG. 33 (Case 13). Coronal sections of the brain showing (a) (Upper) the tumor in the proximity of the optic chiasm and (b) (Lower) the tumor within the third ventricle.

*Necropsy findings. Gross:* At autopsy multiple pulmonary emboli and infarcts of the lung were found. A confluent bronchopneumonia in the bases of both lungs was present.

*Brain:* In the region of the floor of the third ventricle there was a smooth greenish yellow mass filling the interpeduncular space; this mass appeared to be continuous with the indubulum. The posterior communicating arteries were displaced laterally by the mass;



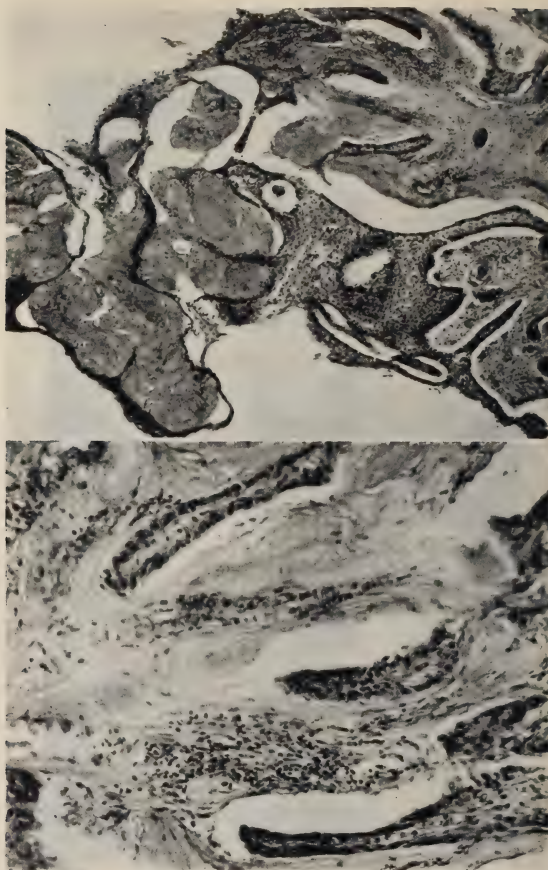


FIG. 34a (Upper) (Case 13). Section of the tumor showing bands of stratified squamous epithelium and the enclosed hyalinized connective tissue. Hematoxylin and eosin stain.  
FIG. 34b (Lower) (Case 13). Section of the tumor showing embryonal hair follicles. Hematoxylin and eosin stain.

otherwise the arteries at the base of the brain appeared normal. The pituitary body appeared normal in size and consistency.

On sectioning of the brain, there was very marked bilaterally symmetrical internal



hydrocephalus affecting all the ventricular subdivisions including the aqueduct and fourth ventricle. In the interpeduncular space there was a fairly large mass of neoplastic tissue which on sectioning seemed to be continuous with the *pituitary body*, although a line of demarcation could be seen between the tissue and what was left of the normal pituitary. The tumor was closely adherent to the optic chiasm and the optic tracts directly posterior to the optic chiasm. Posteriorly this tumor could be traced into the third ventricle and found projecting slightly to the right in the front of the anterior pillar of the fornix filling the entire hypothalamic part of the third ventricle and extending dorsad (fig. 33). The tumor had a yellowish gray appearance; in the inferior surface it seemed to be covered by a number of little seed-like granules. Its cut surface also showed a coarse granular appearance.

*Microscopic observations:* Sections of the tumor, stained with hematoxylin and eosin, revealed, as its main histologic feature, long and irregularly arranged sheaths of stratified squamous epithelium (fig. 34a), carrying with it, and in parts enclosing, a layer of

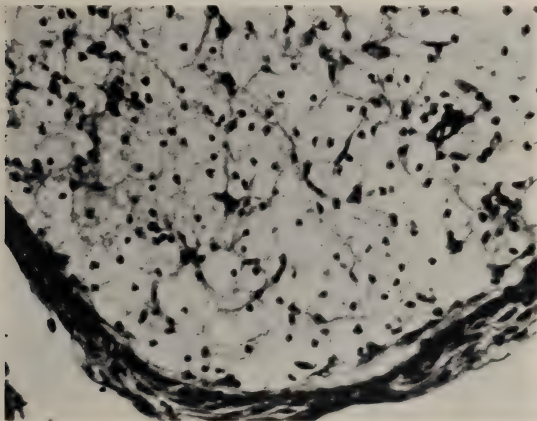


FIG. 35 (Case 13). Section of the tumor showing the cells simulating those of sebaceous glands. Hematoxylin and eosin stain.

fibrous connective tissue containing a considerable amount of homogeneous collagenous material and thin walled blood vessels. Some such vessels contained dense collections of small round cells. In some parts the stratified thinned epithelium was arranged, giving rise to villus-like projections within the core of which there were many large cells in the pale nuclei and finely granular cytoplasm. In other parts of the tumor, there were epithelial columns imbedded in a homogeneous connective tissue substance simulating hair follicle formation (fig. 34b), while in other parts there was a well segregated and well encapsulated collection of cells (fig. 35) which duplicated in all essentials the cells exhibited in Figure 4 in Case 1, which bore a strong resemblance to cells encountered in sebaceous glands.

Sections through the anterior lobe of the pituitary body disclosed tumor tissue of a character similar to that found in the main tumor mass. It was found lodged in a groove on the dorsal surface of the pituitary body, separated by a capsule displaying no invasive tendencies. The pituitary itself was flattened and compressed. Many of the cells showed

disintegrating changes, but most of the anterior lobe showed only mild degenerative alteration.

*Comment.* In this case the tumor is grossly solid but on microscopic investigation it is found to consist of squamous epithelial bands enveloping fairly solid cords of connective tissue. Within the latter there are encountered foreign body giant cells, numerous areas of hornified epithelium, large groups of cells suggesting the structure of sebaceous glands and scattered papillae with suggestive structure of primitive hair follicles. The occurrence of the tumor in a man, aged 42 years, is of clinical significance.

This tumor as in the preceding case is best grouped with the solid form of hypophyseal duct tumor of the craniopharyngeoma variety.

*Case 14. Solid hypophyseal duct tumor (craniopharyngeoma) in a man aged 54 years. Early symptoms, fatigability, somnolence and severe headaches. Blurred and double vision. Focal signs. Ventriculography showed failure of anterior part of third ventricle field. Craniotomy, tumor in the floor of the right lateral ventricle removed. Rapid decline, exitus.*

*History:* H. G. (P.M. #12154), a man, aged 54 years, was apparently well until six months before entering the hospital, when he developed increasing fatigue, drowsiness and memory impairment. Two months later he became subject to severe frontal headaches which were worse in the morning and occurred four to five times a week. At about the same time his vision became blurred and he complained of double vision. At times the left side of his visual field appeared black.

*Examination:* The patient was mentally dull. Recent memory was definitely impaired. There was some difficulty in recalling names but there was no definite aphasia. The margins of the right disc were blurred in the upper nasal portion. Vision was impaired in both eyes; objects and color were recognized better in the nasal than in the temporal fields. The left palpebral fissure was larger than the right. A slight facial asymmetry, apparently mimetic in character was present. There was slightly less sustained effort in the left arm than in the right arm. The biceps jerks were slightly more active on the left side. The sense of pain was diminished on the left side, involving the face, trunk and extremities. The blood pressure was 170 systolic and 110 diastolic. The pulse rate was 48 per minute.

*Laboratory data:* Blood cytology, chemistry and Wassermann reaction were negative. Urine, negative. Basal metabolic rate was minus 33 per cent. X-ray examinations of the skull and chest were negative. Electroencephalographic studies yielded no positive findings. Lumbar puncture yielded cerebrospinal fluid under an initial pressure of 135 mm. of water with normal dynamics. The fluid was bloody. When centrifuged, however, the supernatant fluid was colorless.

*Course:* The diagnosis of a thalamo-hypothalamic lesion on the right side was made. On the ninth day in the hospital a left frontal ventriculography was performed. It showed considerable dilatation of both lateral ventricles and the third ventricle, but the anterior portion of the third ventricle filled poorly; the fourth ventricle was not visualized. Four days later a right frontal craniotomy was performed. Through a transventricular approach a large firm tumor was removed from the floor of the right lateral ventricle. Following the operation the patient developed a left hemiparesis; his temperature rose to 103°F.; the blood pressure began to drop and despite all supportive measures, the patient expired on the second post-operative day.

*Surgical specimen:* The specimen consisted of several small irregular pieces of reddish yellow tissue with a total weight of 7.5 Gm.; the largest piece measured 2 x 2 x 1 cm. Some portions of the tissue were solid and appeared lobulated; other portions were cystic and were surrounded by a thin smooth membrane. Some fragments of tissue consisted of many small cysts having the appearance of a bunch of grapes. The tissue in general appeared

to be moderately vascular. About 1 cc. of yellow cloudy fluid was also received (this was obtained by aspiration of the tumor mass at the time of operation).

Sections of the surgical material stained with hematoxylin and eosin revealed densely cellular tumor tissue composed of irregular collections of stratified squamous epithelium with a well defined basal layer (fig. 36) surrounding large cores of loose connective tissue which contained a moderate number of thin walled blood vessels. The connective tissue core had a myxomatous appearance and was composed primarily of loosely arranged fusiform cells among which were scattered small round cells, polymorphonuclear leucocytes and phagocytic cells; within the connective tissue cores there were also some round empty spaces having the appearance of vacuoles. At the periphery of the tumor tissue there were a few areas of hemorrhage.

*Necropsy findings. Brain.* *Gross:* Under the bone flap there was an area of extradural blood clot corresponding in size to the defect in the skull and measuring about  $\frac{1}{4}$  inch in

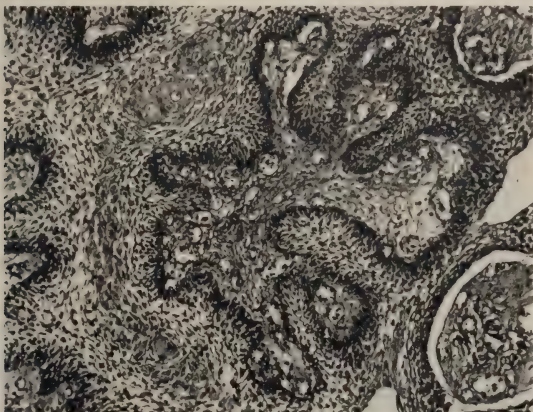


FIG. 36 (Case 14). Histologic structure of the tumor (see text). Hematoxylin and eosin stain.

thickness; there was no moulding of the right cerebral hemisphere due to the blood clot. The dura under this was somewhat adherent to the brain. There was a moderate increase in the subarachnoid fluid diffusely over the left cerebral hemisphere. In the region of the interpeduncular space there was a dark red smooth mass projecting from the inferior surface of the brain and measuring about 2 cm. in diameter.

The *pituitary gland* showed no abnormalities.

On sectioning of the brain, a marked defect was seen in the right hemisphere in the middle of the frontal lobe extending from the surface at the level of the middle of the second frontal convolution, inward and widening on its way to communicate with the lateral ventricle on the same side. This defect was bordered on its sides by an area of discoloration, widening as it extended inward toward the ventricles. The discolored area represented friable softened tissue. At that level of the septum pellucidum was a marked thickening and apparently occupied by tumor tissue. In the depth of this defect there was a large excavation which, in all probability, represented an area from which tumor tissue was

removed at operation. Further back on the level of the optic chiasm an area of discoloration, probably tumor tissue, was found to involve almost the entire head of the caudate nucleus and part of the adjacent thalamus. The internal capsule was still visible although there was also some discoloration. The hypothalamic region was discolored on both sides and part of the optic chiasm seemed to be invaded by this discoloration. The corpus callosum on its ventral aspect was also softened and gave the impression of being invaded by tumor tissue extending to the septum pellucidum. The ventricles were free of blood.

*Microscopic observations:* Sections through the anterior portion of the third ventricle stained with hematoxylin and eosin revealed considerable disorganization of tissue and large areas of hemorrhage in the tissues surrounding the ventricle. In some portions of the disorganized area there were large collections of polymorphonuclear leucocytes. No tumor cells were seen.

Sections through the pituitary body stained with hematoxylin and eosin revealed large necrotic areas in the anterior lobe; in some portions of the necrotic areas there were dense collections of polymorphonuclear leucocytes. There were only a few areas within the anterior lobe in which the glandular tissue was fairly well preserved.

Sections of the cerebral cortex stained with hematoxylin and eosin revealed slight thickening of the smaller blood vessels throughout the cortex. Otherwise there were no significant abnormalities.

*Comment.* Of particular interest in this case is the solid character of the tumor, as in the preceding two instances, though the microscopic structure is that of a cystic hypophyseal duct neoplasm. It contains bands of stratified squamous epithelium of a fairly primitive type overlying collections of poorly differentiated connective tissue cells with scattered small collections of young cartilaginous cells.

#### SUMMARIZED ANALYSIS OF CLINICAL MANIFESTATIONS AND SELECTED FEATURES

*Age Incidence:* The impression is gained from a review of the literature that this type of tumor is encountered more commonly in the younger age groups. Frazier and Alpers (19) found that 70 per cent of the adamantinomata studied by them occurred in patients under 20 years of age. They stated that the youngest recorded patient revealing this type of tumor, reported by Olivecrona, was 5 years of age. Cushing (10), however, later included in the group of craniopharyngeoma reported by him one patient  $3\frac{1}{2}$  years of age, and several over 60 years of age. Bailey and his co-workers (11), in a survey of 138 cases collected from the literature, have also found that these tumors, "although common in childhood are by no means confined to this age period." He found that symptoms in the cases of the reviewed group began at the following periods: 0-10, 20 cases; 10-20, 46 cases; 20-30, 27 cases; 30-40, 20 cases; 40-50, 12 cases; 50-60, 9 cases; and over 60 years, 4 cases. Our series also demonstrates the great range in age incidence. Two of our patients (Cases 2,3) were only  $3\frac{1}{2}$  years of age on admission to the hospital, and one of them had exhibited signs of an intracranial lesion at the age of 13 months. In both instances, the tumor was of the cystic variety. The oldest patient in our series (Case 14) was 54 years of age. Two other patients were over 40 years of age (Cases 9,13), and the others were distributed according to age on admission as shown in the accompanying table.



| <i>Age on Admission</i> | <i>Number of Cases</i> |
|-------------------------|------------------------|
| 1-10                    | 5                      |
| 11-20                   | 3                      |
| 21-30                   | 2                      |
| 31-40                   | 1                      |
| 41-50                   | 2                      |
| 51                      | 1                      |

*Sex:* As already noted by other investigators, there is no significant variation in sex rate incidence. In fact, in our material there is equal distribution between the two sexes.

*Trauma:* Three of the patients gave a history of trauma to the head shortly before the onset of symptoms. There was no reason to believe that there was anything but a coincidental relationship between the trauma and the development of the tumor. In a previous study, one of us has already pointed out that trauma plays a very doubtful role in the development of cerebral neoplasm (21).

*Onset:* The initial symptom in one of our patients (Case 3) was a convulsive episode, followed by visual disturbances. The convulsions were associated with an acute febrile disease, however, and may have assumed a role in the disease process under discussion only by drawing attention to the visual disturbances. In all other cases, there was a gradual onset of symptoms. In no case was the patient aware of the disease process for more than about 5 years. On the other hand, symptoms had been in progress for considerable periods of time (as long as 5 years) before any of the patients was hospitalized.

The initial symptoms varied. Signs of increased intracranial pressure were the most common presenting complaints, particularly headaches and vomiting. Visual disturbances, reduction or loss of vision and diplopia were more prominent initial complaints in 4 cases (Cases 3,4,9,13). Vegetative disturbances, particularly obesity, disturbance in water balance, abnormal secondary sexual characteristics and somnolence appeared early in all cases except Case 9.

*General Manifestations of Increased Intracranial Tension: Headache* was a manifestation common to all observed cases. No general statement can be made as to the location of headache—except to say that in itself it has no localizing value.

*Vomiting* was another frequent symptom, occurring in almost all of the cases observed at some time during the clinical course.

*Papilledema and Optic Atrophy:* While the former is considered as due to increased intracranial tension, the latter is in many instances the result of direct pressure of the tumor upon the optic chiasm, tracts or nerves. They are considered together under this heading for convenience only.

Fully developed papilledema affecting both discs was present in only 5 cases (Cases 4,6,7,8,12). Three cases disclosed slight papilledema (Cases 5,13,14). Optic atrophy, on the other hand, was noted in six cases (Cases 2,3,6,8,10,13), two of which (Cases 6,8) had also shown papilledema. Two cases exhibited neither papilledema nor optic atrophy (Cases 1,9).

No deductions could be made as to the relationship of the site of the tumor



to the development of papilledema or primary optic atrophy, nor does the age of the patient bear any relationship to these two variants in the implication of the optic nerves.

*Extrinsic Ocular Manifestations:* Some disturbances in the extrinsic ocular mechanism were present in ten cases (Cases 1,2,3,5,7,8,9,10,11,14), although these were neither a common early complaint nor a prominent feature in the further course of the patient. They varied from involvement of a single muscle to complete bilateral third nerve palsy (Case 9). Ptosis was described in six cases (Cases 1,2,5,8,9,14), unilateral in each case except Case 9. The individual muscles involved included the internal rectus (Cases 1,2,8) and superior rectus (Case 3). One patient (Case 9) displayed bilateral oculomotor nerve palsy as well as a right abducens palsy. Conjugate deviation of the eyes was present in one case (Case 11) and deficient conjugate movement of the eyes in another (Case 5). Pupillary abnormalities were present in five of the cases (Cases 1,5,7,9,11), the manifestations including minor inequalities of pupillary diameter to complete fixation of a dilated pupil. Proptosis was present in one case (Case 5).

*Visual Field Disturbance:* Great variation in the extent of visual field defects is encountered in this type of tumor. In this respect this type of tumor behaves much like any other tumor in this location (22). The records of our patients unfortunately do not contain information concerning the visual field disturbances in each case. Among the cases adequately studied from this point of view, temporal field defects, either unilateral or bilateral, were the most commonly encountered type of defect (Cases 2,4,8,13,14) with homonymous hemianopsia present in two cases (Cases 7,10).

*Visual Acuity:* Diminution of vision was not only a frequent early symptom but also a common finding, with significant asymmetry in the reduction of the acuity of vision in the clinical course. Complete terminal amaurosis was encountered in only one case (Case 8). One patient (Case 13) displayed "islands" of micropsia and teleopsia.

*Vegetative Disturbances:* Of great clinical significance and an aid in the localization of the lesion were the several vegetative disturbances. Seven patients manifested polydipsia and polyuria (Cases 1,2,3,5,6,12,13). Gastrointestinal complaints, including constipation (Case 1), anorexia (Cases 1,2,3,8), and epigastric pain (Cases 2,12) were not without importance. Although weight loss naturally accompanied the anorexia in the four cases in which the latter was present, obesity was found in five patients (Cases 3,4,6,11,12), several of whom were described as "Froehlich type", associated with hypogonadism and underdeveloped secondary sexual characteristics. A disturbance in hair distribution was noted in several cases, with lanugo hair described in one case (Case 1) and loss of axillary and pubic hair at the age of 20 constituting an early symptom of another patient (Case 8). Amenorrhea was a prominent complaint among the female patients. In only one case (Case 13) were mild acromegalic features described; this patient proved to have a suprasellar solid tumor, at variance with the findings of Crichtley and his co-workers (13) that acromegaly

occurred only among the group of intrasellar tumors. In our case the pituitary gland itself was intact. In agreement with the findings of Frazier and Alpers (17), in the few cases in whom basal metabolic rates were determined, negative values were obtained.

The foregoing constellation of symptoms and signs, which we have grouped under the heading of vegetative disturbances have most frequently been referred to in the literature as endocrine and particularly "pituitary" in origin. In the majority of cases studied, the pituitary body was only moderately affected by compression. In only one instance (Case 2) was it not found; in another instance (Case 8) no grossly recognizable pituitary tissue was found but histologically, a few remnants were discovered at the periphery of the tumor; in a third instance (Case 10) a small nodule of tissue measuring about 3 mm. in its long diameter was all that was left of the pituitary, while in the fourth instance (Case 11) a yellowish, cheesy granular material in the depth of the sella turcica was all that was left of the pituitary body. On the other hand, since most of the tumors extended for a considerable distance in the suprasellar region, they compressed and in all probability disturbed the normal function of the hypothalamic structures. A similar situation was noted by one of us, Globus (23), in the study of pineal tumors. It was found there that the vegetative phenomena, which are exhibited by patients with pineal tumors, are not due to specific pineal hormonal effects (since they are present only in a small number of pinealomas) but are, most likely, due to involvement of vegetative centers in the hypothalamus by either direct invasion or secondary pressure effects.

*Pulse and Temperature Dissociation:* A form of discord between the temperature curve and that of the pulse rate was noted in some cases. It points to a disturbance in the heat regulating mechanism, which has its seat in the hypothalamus and the neighboring vasomotor regulating centre. The type of dissociation in which the pulse rate does not follow the fluctuations in temperature was a condition already noted in a previous communication (24) in which it was pointed out that tumors (and probably other types of lesion) in the hypothalamic region are likely to produce this disorder. It may thus be considered as a significant localizing sign.

*Miscellaneous Neurological Findings:* Many findings suggested involvement of various regions of the central nervous system, both near to and distant from the site of the primary pathology. *Pyramidal tract signs*, such as Babinski or Hoffman signs, absent abdominal reflexes and variations in the strength of deep tendon reflexes were present in 10 cases (Cases 1,2,3,4,5,7,8,10,11,14). Cerebellar signs, including generalized hypotonia, tremor, and unsteady gait were found in three cases (Cases 6,9,10). One patient (Case 12) complained of olfactory dulling and gustatory hallucinations. Dulling of intellect was noted in several cases, but no psychometric studies were done. In 8 cases unilateral central facial weakness was described (Cases 1,2,5,8,9,10,11,14). Frequent attacks of decerebrate rigidity were a prominent feature of one case (Case 10) and hemisensory disturbances were present in 2 cases (Cases 11,14).

*Cerebrospinal Fluid:* Cerebrospinal fluid studies were made in eleven cases.

No consistent abnormalities were found. Pressure was elevated beyond normal limits in only one case (Case 5). Protein content was increased in two cases (Cases 5,13). Pleocytosis was found in one case which showed 480 mononuclear cells per cu. mm. of cerebrospinal fluid (Case 10), one 200 cells (Case 8), one 10 cells (Case 7), and one 8 cells (Case 13), with no bacterial organisms found, suggesting a sterile (reactive) meningitis due to irritation of the meninges by the cyst contents.

*X-ray Findings:* X-ray studies of the skull were done on 13 of the patients. All of the patients except three (Cases 11,12,13) showed changes in the sella turcica varying from erosion of the clinoid processes to diffuse enlargement of the sella. Abnormal calcifications were described in 7 patients (Cases 2,3,4,5,6,7,8) located in the suprasellar region. Calcifications were present within the sella as well as above it in one case (Case 2). Air studies were done on 6 patients, 5 of whom were found to have dilated lateral ventricles (Cases 5,7,12,13,14). The third ventricle was dilated in 2 of the patients (Cases 5,14). In the other cases studied, the third ventricle either did not fill at all or showed a definite filling defect. In one case (Case 9) in whom the third ventricle was not outlined, it was reported that the aqueduct was visualized and displaced posteriorly.

*Radiotherapy:* Deep x-ray therapy was administered to three cases (Cases 3,5,8). In one instance (Case 5) no improvement was noted. In another (Case 3), there was a brief subsidence of some of the symptoms. In a third instance (Case 8), there was significant abatement of all symptoms, including an increase in the visual fields for a period of one year.

*Surgical Intervention:* Operative intervention was attempted in all of the cases; in Case 10, only a ventricular aspiration was carried out. In 3 cases (Cases 1,9,13), because of the poor condition of the patients during the procedure, the operation was interrupted before completion. In 2 cases (Cases 11,12) the tumor was not found at operation. In all other cases, the cyst contents were evacuated and accessible portions of the tumor were removed.

*Survival Periods:* Six patients (Cases 1,4,6,12,13,14) died within the immediate post-operative period following their first operation at The Mount Sinai Hospital. One of these (Case 6) had had a previous craniotomy at another hospital. In three of the cases (Cases 4,6,14), the operation had apparently been a procedure with no untoward occurrences, yet marked post-operative hyperthermia developed. Three patients (Cases 8,9,11) showed improvement for several months after operation, although no tumor had been found in one of these cases (Case 11), and the operation had been interrupted in another (Case 9).

One patient (Case 2) died 2 years after operation, from a mastoid infection. One case (Case 3) survived for 5½ years, post-operatively; at that time she showed recurrence of signs with greater severity. Subsequently, contact with the patient was lost. The longest survival period in our series was 9 years, in a child (Case 7) who had had a decompression and two subsequent craniotomies for partial removal of the cyst wall.

From the foregoing statement, it is obvious that operative intervention contributed very little in establishing a lasting or permanent cure, in spite of the fact that we are dealing with a tumor that can be accurately recognized and its character identified in fairly early clinical stages of its development. It would seem as Bailey and his co-workers (11) said that in the great majority of instances the tumor appears to be of a benign character and seems to meet the favorable conditions for the surgeon. Despite this, Cushing (10) felt that "until some method is devised whereby the usually multilocular epithelial lesion can be destroyed or inactivated *in situ* the mortality will doubtless remain high." A similar gloomy outlook as to the expectation of life in the majority of such cases was expressed by Frazier (12).

#### SUMMARY OF ANATOMICAL OBSERVATIONS

The gross appearance of the hypophyseal duct tumors varied slightly, the exposed surface being somewhat round or elliptical in outline. When cystic, these tumors were provided with a fairly thick capsule readily recognized in the exposed parts, but to a large extent, hidden from view where it was intimately adherent to adjacent brain tissue from which it could not be separated without destruction of brain substance.

On the average the tumors were quite large, occupying the entire interpeduncular space, often extending rostrad beyond the optic chiasm and by their dorsal expansion raised the floor of the third ventricle or broke through it to invade the ventricle. The structures within the interpeduncular space were usually compressed, flattened and often displaced. Frequently, they were adherent to the tumor. This was particularly true of the optic chiasm, optic tracts and oculomotor nerves. Where the floor of the third ventricle was displaced upward, structures such as mammillary bodies and the tuber cinereum were deformed or altogether lost their identity.

As already mentioned, the tumors were more frequently of the cystic variety while a considerable number were of the solid type. When cystic, they usually contained a greenish or yellowish brown viscid fluid. Many such cysts exhibited in one or more parts of the wall islands of solid tumor tissue and areas of calcification.

The solid tumors, the so-called adamantinomas, which often contained a few scattered cysts, were less likely to be enveloped by distinct capsule and in parts where they were in relation to the floor of the third ventricle, they have fused with brain tissue and often broke through it to enter the third ventricle. Within that ventricle, they presented the appearance of a papillary growth. Not infrequently the third ventricle was fully occupied by the tumor and the floor of the ventricle was no longer recognizable and probably entirely replaced by tumor tissue.

*Histologic features:* The greater number of tumors, as already mentioned, were of the cystic variety and disclosed a fairly uniform histologic character, that of a simple papillary cyst. The wall of the cyst consisted of a layer of connective tissue lined by a regular band of stratified squamous epithelium in

various stages of development and various phases of degeneration. The lining gave rise to numerous verrucous nodules consisting of heaps of squamous epithelial cells projecting into the cystic cavity. Alternating with this there were, in some instances, collections of cells simulating hair follicles, and other collections of cells suggested epithelial pearl formations. Within the connective tissue substratum, as well as in the adjacent hyalinized tissue, foreign body giant cells were often encountered, and characteristic spaces of dissolved cholesterol crystals were numerous.

Several of these tumors contained within the thicker parts of the wall many embryonal residues simulating cartilage, bone, hair follicles, sebaceous cells, acinar structures simulating those of the pars intermedia and enamel organ in various stages of development. The presence of the structures simulating enamel organ primordia made it difficult to draw a sharp line of demarcation between the simple papillary cyst and the solid form of hypophyseal duct tumors, the adamantinomas. The latter, where fully developed, presented features in striking contrast to the cystic tumors. They contained tracts, sheaths, and narrow bands of squamous epithelium. The latter appeared to branch and anastomose, forming complicated structural designs. The dominant cellular elements by their form and arrangement bore a strong resemblance to the embryonal enamel organ. In the more typical areas, there could be discerned a basilar layer of columnar cells (the ameloblasts), a layer simulating the stratum intermedium and another layer consisting of the so-called stellate cells. A frequent occurrence in this type of tumor, and somewhat less common in the cystic tumors were glandular structures bearing strong resemblance to the acini characteristic of the pars intermedia in the mature pituitary body. In addition, there was an abundance of supporting tissue consisting of fibrous material often hyalinized.

*Embryologic considerations:* Attention was already called in foregoing pages that the tumors under consideration have their origin in residues of the cranio-oral (pharyngeal) duct. These residues are in the nature of aggregations of epithelial cells which have strayed away from their point of origin to the surface of the infundibular stalk at its junction with the hypophysis. These residues form lower and upper groups and attempts have been made to distinguish between tumors presumably derived from lower and those arising from upper group cells. Those derived from the lower group remain within the sella turcica. Those arising from the upper group are said to form above the sella turcica. From there they extend upward, raising the floor of the third ventricle, often completely occluding it. It is also said that the former constitute the majority of cases. None of these observations are borne out by the findings in our material or by a survey of material reported elsewhere. It seems, as shown by our material, that no distinction can be made between tumors derived from one or another group of cells, much as it would be desirable to consider the cystic tumors as those arising from an upper cell group and the solid tumors from a lower cell group. While the latter are more likely to be of the adamantinomatous character, and contain structures pointing to an origin



from primordia lower in the cranio-oral tract, it, nevertheless, is not possible to go beyond an assumption.

*Pituitary body:* The pituitary bodies in a large number of cases were within fairly normal limits. In only a few cases were they compressed showing evidence of disintegration. In one case (Case 2) there was no record of the presence of the pituitary and no vestige of the gland was noted in the wall of the cyst (no serial sections were cut). A similar condition was found in Case 11 where the pituitary was replaced by yellowish cheesy material while in two other cases (Cases 8,10) very small remnants of pituitary tissue were all that was found.

#### CONCLUSIONS

1. Fourteen cases of hypophyseal duct tumor are described.
2. The tumors were found to be derived from residues of the so-called cranio-pharyngeal (cranio-oral) duct.
3. The tumors were subgrouped as cystic and solid; and in each subgroup there were those which were identified as papillomatous and those which were partially or dominantly adamantinomatous.
4. The tumors often implicated the floor of the third ventricle, or broke through it to expand into the third ventricle, thereby causing hypothalamic disorders.
5. Clinically, the recorded cases presented constellations of symptoms and signs which offered substantial diagnostic leads. Among the latter, in order of their significance and in varying degree, were:
  - (a) Vegetative disturbances, such as retarded growth, disturbance in fat distribution with occasional underdevelopment of secondary sex characteristics (Froelich's syndrome), imbalance in water metabolism (polydipsia and polyuria), amenorrhea, loss of libido, pulse and temperature discord, anorexia, obstinate constipation.
  - (b) General manifestation of increased intracranial tension, which included headache, accompanied by nausea and vomiting, papilledema and mental retardation.
  - (c) Signs due to direct pressure by tumor: optic atrophy, loss of acuity of vision, hemianopic field defects, pyramidal and cerebellar signs.
  - (d) X-ray findings, consisting of calcifications in or about the sella turcica.
6. Surgical intervention in many instances resulted in but temporary relief and at best, in a relatively longer survival period.

#### BIBLIOGRAPHY

1. GLOBUS, J. H.: Teratoid Cyst of the Hypophysis. *Arch. Neurol. & Psychiat.*, 9: 4, 417, 1923.
2. MUELLER, J.: Ueber den feineren Bau und die Formen der krankhaften Geschwülste. Ed. 1, 1838, p. 50.
3. VIRCHOW, R.: Ueber Perlgeschwülste (Cholesteatome Mueller). *Virchows Arch. f. path. Anat.*, 8: 371, 1855.
4. CRUVEILHIER, J.: Anatomie pathologique du corps humaine. Vol. 2, bk. 2, plate 6.
5. REMAK, R.: Cited by Erdheim (see reference 9).

6. BONORDEN, H. G.: Ueber ein meningeales Cholesteatom mit Haaren und Talgdrüsen. *Beitr. Z. path. Anat. u. z. allg. Path.*, 11: 593, 1892.
7. BENEKE, F. W.: Zur Frage der meningealen Cholesteatome. *Virchows Arch. f. path. Anat.*, vol. 142, 1895.  
——— Zur Frage der meningealen Cholesteatome und Berichtigung. *Virchows Arch. f. path. Anat.*, 149: 95, 1897.
8. BOSTROEM, E.: Ueber piale Epidermoide, Dermoide und Lipome und durale Dermoide. *Zentralbl. f. allg. Path. u. path. Anat.*, 8: 1, 1897.
9. ERDHEIM, J.: Ueber Hypophysengangsgeschwülste und Hirncholesteatome. *Sitzungsb. d. k. Akad. d. Wissensch.*, 113: 537, 1904.
10. CUSHING, H.: *Intracranial Tumors*. Springfield, Illinois, Charles Thomas & Co., 1932, p. 150.
11. BAILEY, P., BUCHANAN, D. N., AND BUCY, P. C.: *Intracranial Tumors of Infancy and Childhood*. Chicago, Illinois, The University of Chicago Press, 1939, p. 598.
12. FRAZIER, C. H.: Brain Tumors in Children. *Arch. Pediat.*, 53: 295, 1936.
13. FARNELL, F. J.: An Extracerebral Tumor in the Region of the Hypophysis. *New York M. J.*, 93: 462, 1911.
14. DUFFY, W. C.: Hypophyseal Duct Tumors. *Ann. Surg.*, 72: 537, 1920.
15. CRITCHLEY, M., AND IRONSIDE, R. N.: The Pituitary Adamantinomata. *Brain*, 49: 437, 1926.
16. PEET, M. M.: Pituitary Adamantinomas. *Arch. Surg.*, 15: 6, 829, 1927.
17. BECKMAN, J. W., AND KUBIE, L. S.: A Clinical Study of Twenty-One Cases of Tumour of the Hypophyseal Stalk. *Brain*, 52: 127, 1929.
18. BAILEY, P.: Note concerning Keratin and Keratohyalin in Tumors of the Hypophyseal Duct. *Ann. Surg.*, 74: 501, 1921.
19. FRAZIER, C. H., AND ALPERS, B. J.: Tumors of Rathke's Cleft. *Arch. Neurol. & Psychiat.*, 32: 972, 1934.
20. MACCALLUM, W. G.: Adamantinoma of the Hypophyseal Duct. *J. Mt. Sinai Hosp.*, 8: 5, 798, 1942.
21. GLOBUS, J. H., AND SAPIRSTEIN, M.: Massive Hemorrhage into Brain Tumor. *J.A.M.A.*, 120: 348, 1942.
22. GLOBUS, J. H.: Diagnostic Value of Defects in the Visual Fields and Other Ocular Disturbances. *Arch. Ophthalm.*, 14: 325, 1935.
23. BING, J. F., GLOBUS, J. H., AND SIMON, H.: Pubertas Praecox: A Survey of the Reported Cases and Verified Anatomical Findings with Particular Reference to Tumors of the Pineal Body. *J. Mt. Sinai Hosp.*, 4: 935, 1938.
24. STRAUSS, I., AND GLOBUS, J. H.: Tumor of the Brain with Disturbance in Temperature Regulation. *Arch. Neurol. & Psychiat.*, 25: 506, 1931.

# ASTHMA SYNDROME ASSOCIATED WITH ANOXEMIA, HEPATIC AND RENAL INVOLVEMENT

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## CASE HISTORY

*History:* A house wife, aged 46 years, was admitted to The Mount Sinai Hospital on February 12, 1943 in a state of coma of sixteen hours duration. It was said by members of the family that with the exception of a non-productive cough which began 14 months ago, the patient had had no previous illness. The cough disappeared for a short period, and about 8 months prior to admission she developed pain in the right side of the chest and fever. This was diagnosed as pleurisy and she was confined to bed for 2 months. She made a fair recovery but soon thereafter began to exhibit wheezing respirations suggestive of bronchial asthma. Adrenalin was ineffective in controlling the asthmatic attacks. Various skin tests failed to reveal an allergic etiology. Bronchoscopy did not disclose any abnormalities in the trachea or bronchi at the time of the examination. In September 1942 she began to experience substernal pain which at first intermittent in character became progressively worse. On the evening of February 11, 1943 when seen at her home she appeared to be in status asthmaticus. It was said that this condition began the day before when after a fit of coughing she suddenly developed dyspnoea, cyanosis and wheezing respiration. Inasmuch as the usual therapeutic measures such as epinephrine 1:1000, epinephrine in oil, etc. proved of no avail in controlling the symptoms, her physician administered 20 cc. of ether in oil, for the purpose of sedation. Although most of this was expelled, the patient went into a shock from which she recovered in about 30 minutes. On regaining consciousness she remained in respiratory distress.

At this time on physical examination the patient appeared markedly cyanosed and gasping for breath. The respirations were shallow and rapid with a rate of 40-50 per minute. Her chest appeared distended and on percussion was tympanitic throughout. Auscultation disclosed generalized sonorous rales indistinguishable from those of true bacterial asthma. Her heart showed no abnormalities, but the pulse was rapid. She answered questions rationally although with difficulty, due to the embarrassment in her breathing. She pointed to the upper part of the sternum as the seat of the greatest discomfort.

In an attempt to give relief, she received within the space of two hours,  $\frac{1}{2}$  grain of papaverin, 100 mg. of nicotinic acid intravenously, 0.5 cc. of epinephrine 1:1000, 1 cc. of epinephrine in oil as well as 10 cc. of aminophyllin intravenously without the slightest effect. The dyspnoea and the wheezing respiration continued even though oxygen was continuously administered through a nasal catheter. It was therefore decided that sedation was the treatment of choice and the patient was given 3 grains of seconal and 3 grains of sodium amytal by mouth. Following this she gradually became somnolent and lapsed into unconsciousness. The following day, February 12, 1943, she was brought to The Mount Sinai Hospital.

*Examination:* On admission she was in a stuporous state, with manifest cyanosis and wheezing respiration. Physical examination showed the neck veins distended, the trachea was shifted to the left and the respiratory movements of the left side of the chest were very much diminished. On percussion that side as compared with the right presented marked tympany both anteriorly and posteriorly. The resonance at the right base was impaired. On auscultation coarse rales and wheezing respiration were especially audible over the right lung. There was a diminution in the breath sounds over the left lung. The heart was in the normal position and the sounds were of good quality. The blood pressure was 100 systolic and 60 diastolic. The liver was palpable 2 fingers below the costal margin. The rest of the examination was negative except for absence of deep reflexes.

*Course:* The history of continuous wheezing and the shifting of the trachea to the left together with the restricted respiration of the left chest suggested the possibility of tracheal obstruction. Since the x-ray examination which was made immediately on admission showed no abnormality in the lungs, it was decided that she should be bronchoscoped. Bronchoscopy on this occasion disclosed a smooth lobular tumor  $\frac{1}{2}$  cm. above the carina. The mass moved from side to side and seemed to be sucked in alternately to the left and right main bronchus with each inspiration. The tumor appeared to arise from a broad base on the posterior wall of the trachea and proved to be readily removable with very little bleeding. Following this procedure the cyanosis and dyspnoea which had persisted continuously for 36 hours, disappeared almost completely and the patient resumed normal breathing. At this time her temperature had risen to 104°F. and it was decided to give sulphathiazole prophylactically because of the possibility of a complicating pneumonia.

The following morning after only one gram of sulphathiazole had been given intravenously, the blood urea was found to be 36 mg. per cent. The blood chlorides were 610; the carbon dioxide, 48 volumes per cent. The urine showed 2 plus albumin, the presence of urobilin, 1:2 and a few hyalin and granular casts with a moderate number of red blood cells. The hemoglobin was 68 per cent, the red blood cells 3.6 million. The white blood cells 10,950 with 75 per cent segmented polynuclear cells, 8 per cent nonsegmented, lymphocytes 15 per cent and monocytes 1 per cent.

In the belief that her comatose state, in spite of regular respirations, may have been due to barbiturate intoxication, although she had only received six grains in all (3 grains of seconal and 3 of sodium amytal), she was given 6 mg. of picrotoxin intravenously. Following this she opened her eyes, appeared aware of her environment but could not answer questions. The same dose of picrotoxin was repeated on four successive occasions but with no improvement. Throughout the nine days of hospitalization she never fully regained consciousness, except that occasionally she would open her eyes and look about blankly.

A neurological examination did not point to any localizing cerebral lesion. The neurologist, Dr. Joseph H. Globus, expressed the opinion that hypoventilation of the brain coupled with the sedation were probably responsible for the prolonged episode of unconsciousness. The electroencephalogram showed diffuse abnormal cerebral activity with no evidence of any focal lesion.

Treatment consisted of repeated intravenous injections of Ringers solution with calcium gluconate, 10 per cent glucose and blood transfusions, all without any results.

After several days the patient developed fine rales at the base of the left lung, suggestive of pneumonic infiltration. Peculiar bulbous lesions appeared all over the body especially at points of pressure. The temperature remained at high levels ranging between 102° and 104°F. The pulse rate was between 110 and 140 beats per minute. The respiratory rate which had come down to 24 per minute after the removal of the tumor rose three days after admission to between 36 and 40 per minute. She developed edema of the face and back as well as chemosis of the conjunctivae. The urinary output decreased and the blood urea began to mount. Although the uremia had apparently begun before sulphathiazole had been administered in any appreciable quantity, it was thought advisable to exclude anuria due to blockage by sulphathiazole crystals. Cystoscopy however, showed no evidence of obstruction and the urinary flow was present on both sides. The total output of urine increased somewhat following this procedure, but not to any marked extent. On the 17th of February, five days after admission, the total output of urine was 250 cc. in 24 hours. The specific gravity was 1014 and albumin was 2 plus. The blood urea nitrogen on February 14, two days after admission, was 184 mg. per 100 cc. There was no rise in blood pressure which initially showed a systolic of 100 and a diastolic of 60. Three days before exitus there was a sudden appearance of icterus associated with hemorrhagic vesicles and numerous echymosis in various parts of her body. The patient showed distinct evidence of uremia and died on February 20. It was the opinion of Dr. Joseph H. Globus, who re-examined her two days before she died, that the cerebral symptoms were due to an encephalopathy secondary to transient anoxemia.

*Necropsy findings.* The essential gross necropsy findings as reported by Dr. Paul Klemperer were as follows:

*Trachea.* On separating the esophagus from the trachea, a pyramidal tumor was encountered at the posterior and right lateral aspect of the trachea which was intimately connected with the tracheal wall. This measured 4 cm. in length and 2.5 cm. at the base. The tip of this mass was situated near the bifurcation of the trachea. It was well encapsulated, of brownish color and moderately soft consistency. Adherent to it was the vagus nerve. On the inner aspect of the posterior tracheal wall above the bifurcation at the same level as the external tumor mass, there was an area denuded of mucosa. In the base of this two cartilagenous rings were visible which showed irregular edges as if the terminal parts had been resected.

In addition there were present, marked acute pulmonary emphysema and edema of the lungs; bronchopneumonia at the right lower lobe; acute congestion of the liver, spleen and kidneys, necrotizing inflammation of the lower half of the esophageal mucosa; multiple petechiae of the skin and small submucosal hemorrhages in both kidney pelvis, bladder, colon and rectum; moderate hypertrophy of the right ventricle and subicterus.

*Microscopic findings. Trachea.* The tumor of the trachea was found to be an infiltrating cylindroma which ensheathed the vagus nerve.

*Lungs.* There was evidence of marked emphysema and bronchopneumonia in the right lower lobe. The rest of the lung showed congestion, edema and hemorrhages into the alveoli and bronchi.

*Heart.* There was intimal thickening of one coronary branch, otherwise no abnormalities were present.

*Liver.* The main finding consisted of severe congestion of the central portions of the sinusoids, atrophy and disappearance of central zone of liver cell cords and fatty infiltration of the liver cells in the periphery of the lobules. The cytoplasm of the liver cells showed fat globules together with clumps of bile pigment. The nuclei of many cells appeared to be breaking up into small round dark stained fragments.

*Spleen.* There was evidence of marked congestion and decrease in the lymphoid tissue.

*Kidney.* Congestion, edema and definite degeneration of the tubular epithelium in the cortex with vacuolization and disappearance of cells appeared to be present. In addition there were degeneration of the tubular epithelium in the medulla and carryorrhesis with formation of numerous dark round fragments as well as submucosal hemorrhages of the calyces.

*Brain.* The scalp, calvarium and dura were negative. The leptomeninges were clear and glistening. Grossly the brain appeared normal although it was slightly softer than usual. The vessels at the base of the brain, the pituitary gland and the inner ears were negative.

On sectioning, the most striking lesion was found bilaterally and symmetrically within the globus pallidus which showed markedly reduced consistency, and was exceedingly friable with a greyish-red discoloration. This was evidenced in the most internal part of each globus pallidus. The lateral portions as well as the putamen seemed to be intact. Throughout the white substance of both cerebral hemispheres there were small punctate areas of discoloration which seemed to be either minute areas of red softening or areas of extravasation. These were also found within the middle cerebellar peduncle and the tegmentum of the pons.

*Microscopic Description.* "In the region of the globus pallidus there is a large area of very recent rarefaction. There is no apparent reactive phenomenon in the form of gliosis or inflammation. The cerebral cortex elsewhere shows no abnormality. With the Nissl stain, the aforementioned area noted in hematoxylineosin preparation, shows complete cellular depopulation or else they have failed to stain. Patent vessels, although moderately sclerosed, are seen in this area. At the periphery there seems to be an increase in the number of glia; some of which are of the compound granular corpuscle variety."

*Diagnosis.* Encephalomalacia due to anoxemia in the region of the globus pallidus.



## DISCUSSION

Under ordinary circumstances the presence of cough antedating true asthmatic seizures is a frequent occurrence. The original diagnosis of bronchial asthma in this patient was to a certain extent therefore justified, despite negative findings of allergy, especially since bronchoscopy six months prior to admission to the hospital did not reveal any obstructive lesion in the respiratory tract. The negative bronchoscopic findings were probably due to the fact that at the time of the examination the infiltrative lesion of the trachea was insufficiently pronounced to be detected. The bronchospasm responsible for the wheezing respiration simulating true bronchial asthma could therefore not have been due to tracheal obstruction as such, but in the light of the subsequent autopsy findings, to vagal irritation induced by the infiltration of the cylindroma into and about the vagus nerve. That stimulation of the vagus produces bronchial constriction is well known. The gradual invasion of the fibres of the vagus nerve, by tumor cells as observed microscopically, could therefore account for the irritation of this nerve with the resulting cough and the intermittent attacks of asthma in the early phases of the patient's illness, whereas the more or less complete investment of the vagus by the neoplasm would explain the continuous wheezing. The onset of so-called status asthmaticus, unusual in bronchial tumors, was probably due to the combined effect of sud den obstruction at the bifurcation of the trachea and the persistent bronchospasm induced by intense stimulation of the vagus nerve. The reason for the failure of various anti-asthmatic remedies to control the patient's symptoms thus becomes patent. Obviously we were dealing with an "asthma syndrome" due not to edema and spasm of the bronchi on an allergic basis, but to an unusual form of bronchospasm caused by the mechanical and/or possibly chemical irritation of the vagus nerve by the infiltrating growth on the one hand, and intermittent bronchial obstruction by a pendulating mass on the other. This combination of factors proved to be responsible for the interference with the normal respiratory exchange and led to a progressive state of anoxemia. Under such circumstances six grains of barbiturates could be sufficient to accentuate the anoxic state in a brain whose oxidative functions were already depressed, and thus precipitate a state of coma. The ravages of oxygen deficiency were clearly demonstrable in the encephalomalacia observed in the region of globus pallidus.

*Cerebral Changes Due to Anoxemia.* That anoxemia may give rise to degeneration in the central nervous system has been shown by a number investigators. A recent pertinent report by Suggs (1) deals with the case of a 32 year old female patient who had been given 3 grains of nembutal,  $\frac{1}{6}$  grain of morphine sulphate, and  $\frac{1}{150}$  grain of atropin sulphate, prior to nitrous oxide anesthesia for an operation of an incomplete abortion. After 15 minutes of anesthesia, the patient ceased breathing. She was revived within an hour and lived for 41 days in a state of semiconsciousness with a temperature between 101° and 104°F. and pulse of 110 to 140. Various laboratory studies such as urine examination and blood chemistry were found to be negative. At autopsy the most striking finding

consisted of cerebral and basal ganglia degeneration. The remaining organs showed moderate parenchymatous degenerative changes in the kidneys and liver in addition to a lung abscess in the lower right lobe.

*Effect of Oxygen Deficiency on the Liver.* The development of jaundice as a result of anoxemia has been studied by numerous workers, notably Rich and Resnik (2); Rich, Bumstead and Barron (3); Hesse (4), Ladewig (5), Monroe A. McIver (6); Buchner (7) and others. Rich and his associates have demonstrated that simple anoxemia brings about not only atrophic shrinkage of the liver cells but also necrosis of the central live lobules in the absence of heart failure and evidence of passive congestion in the lungs, spleen or any other organs. The cells about the efferent vein in contrast to those in the peripheral region, are definitely more sensitive to the effects of a deficient oxygen supply, just as they are apparently more sensitive than the peripheral cells to the toxic effects of chloroform and other poisons. Rich and Bumstead have also shown that accompanying this liver damage is a concomittant depression of the excretory function of the liver so that its ability to excrete bilirubin injected into the blood stream is impaired. When necrosis of the central liver cells is sufficiently widespread the features of regurgitation jaundice appear because whole bile leaks into the blood from the broken canaliculi in to the necrotic area. Similar liver changes have been described in various anemias and in cases of cardiac decompensation where anoxemia plays the dominant rôle in the development of a retention type of jaundice.

In airmen, who died as a result of anoxemia due to the effect of atmospheric conditions at high altitudes, Ladewig describes round or polyhedric vacuoles in the liver nearest to the acinous centers, which do not contain fat or glycogen. Corresponding alterations could be produced in guinea pigs and rabbits under atmospheric conditions similar to those at high altitudes by keeping animals in low pressure chambers under normal pressure, but reduced oxygen content of the respiratory air. Rossin (8), for example described parenchymatous degeneration and necrosis in the central portions of the lobules in guinea pigs and rabbits subjected to low oxygen tension. Identical liver degeneration has been reported by Hesse in individuals thrown into an anoxic crisis through suffocation or drowning.

*Renal Changes due to Anoxemia.* That oxygen want is also responsible for urinary suppression and uremia, the pathological substrate of which consists of tubular degeneration in the kidneys, has been demonstrated both clinically and at necropsy. The abnormal physiological effects upon the renal output in the case of a healthy male, who overbreathed for 45 minutes and failed to breathe again as he intended to do after the fifth time, has been reported by McCance (9). In this clinical experiment acute anoxemia followed and was sufficiently severe to cause unconsciousness for about 8 minutes. The subject was in a state of collapse for two hours and recovered completely in three hours. During the period of syncope five samples of urine were collected and analyzed with results as follows: 1) The process of ammonia excretion and the ability to concentrate hydrogen ions was unimpaired. 2) The rate of excretion of creatinine and of

sulphates were reduced respectively to three quarters and two thirds of their initial values. 3) The rate of excretion of urea was reduced to one fifteenth of its original value. "Part of this reduction may have been due to great increase in the excretion of ammonia." 4) The rate of excretion of water, sodium, potassium, chlorine and phosphorus was reduced from one fifth to one fifteenth of their original values. 5) Urea clearance fell from 107 per cent of normal to 17 per cent during the period of collapse. It remained subnormal for three hours then rose to 114 per cent.

The theoretical explanation of these observations according to McCance is obscure, because not enough is known of the way urea, creatinine and sulphates are normally excreted and especially how the clearance of these three substances are related to true glomerular clearances. "The fall in the excretion rates of creatinine, urea and sulphates possibly other salt ions coupled with the probability that some fall of blood pressure took place suggest some fault in glomerular filtration."

The basis for the renal disturbances following anoxemia as above described becomes clearer, in the light of the necropsy findings in a series of cases who died from "crush injuries" in the bombing of London as recently reported by Bywaters and Beall (10), Beall (11) and his co-workers; Mayon-Whyte and Solandt (12); Glen (13); Young and McMichael (14) and others. The patients studied ranged in ages from 11 and upwards. The victims were rescued after having been buried for three or more hours under debris from devastated buildings. Some of them had sustained crush injuries to their legs and developed shock, whereas others with the exception of a hematoma in an extremity resulting from an overlying boulder presented no demonstrable injury either to the soft or skeletal tissues. After recovery, as a result of replacement of the circulatory fluids the majority of patients developed oliguria, smoky urine and edema. Death in uremia, with markedly elevated blood urea, followed after about a week in most instances, some few however recovered.

In this connection the clinical and pathological findings in a girl, 11 years of age, pinned under debris for three hours are of pertinent interest. Complete examination in this patient revealed no injury except for a hematoma. She was drowsy, manifesting pitting edema from hip to toes and almost complete anuria except for a few cc. of urine. In spite of treatment the blood proteins decreased from 6.4 to 4.8 mg. The blood pressure rose to 145 systolic and 110 diastolic and the blood urea to 399 mg. per 100 cc. before death. The temperature remained subnormal throughout. At autopsy most of the tubules contained a peculiar debris that stained a brick red color with eosin. The tubules showed marked degeneration, and some of the cells lost their outlines completely. The glomerulae were normal and the capsular spaces were not dilated. In the cases reported by Bywaters, the degenerative changes took place in the proximal convoluted tubules and pigment casts were present in more distant parts. The lungs showed focal hemorrhages and patchy edema, while the liver displayed parenchymatous degeneration and edema in the region of the portal system with dilated lymphatics.

The question whether an unidentified toxic derivative from crushed or necrotic muscles is responsible for the renal damage observed in these cases is excluded by Tomb (15) on the following grounds. 1) The symptoms of renal insufficiency appear early, and are progressive even though the crushed limb is amputated, 2) they are found in cases where no crushing of muscles has occurred, 3) they do not occur as a sequel of infarction or absorption of blood clot (tissue necrosis), 4) it is impossible to establish by cross circulation or other methods, that the blood of an animal suffering from crushing of the limbs (traumatic shock) is toxic (McDowell, (16)).

Manifestations due to anoxemia similar to the renal failure of crush injury, with comparable degenerative changes in the envoluted tubules, which persisted after successful restoration of the circulation by saline infusion, have also been reported by Tomb in association with the anuria in cholera.

It is evident therefore as a result of these observations that oxygen deficiency may induce pathological changes in various organs. In the brain such alterations may be characterized by encephalomalacia, in the liver by a central necrosis of the liver cells, and in the kidney by tubular degeneration. Such tissue changes may be responsible for development of coma, jaundice, anuria and uremia. The presence of similar manifestations in the case under discussion, supported by the post-mortem evidence of encephalomalacia in the region of the globus pallidus, the degeneration of the central zone of the liver cords and tubular epithelium in the cortex and medulla of the kidneys, is strongly suggestive, in the absence of any other etiologic factor, that anoxemia was the most probable cause of this clinical picture. The possibility that the hepato-renal damage may have been caused by the sulphathiazole is unlikely inasmuch as the 1 gm. administered was too small a dose to cause such extensive injury to various organs unless the question of hypersensitiveness to this drug were involved. Inasmuch as there was no history of any drug idiosyncrasy in this case and no authentic record in the literature of similar tissue damage on the basis of sulphathiazole allergy to so small a quantity of this drug, this possibility may be ruled out. Moreover, since the patient had been in coma at least sixteen hours prior to her admission to the hospital the anoxemia antedated the administration of sulphathiazole by twenty-four hours if not longer.

#### SUMMARY

A 46 year old house wife presenting symptoms suggestive of status asthmaticus developed coma following the administration of 3 grains of seconal combined with 3 grains of sodium amytal.

While in this condition evidence of renal insufficiency, uremia and jaundice became apparent.

Necropsy revealed 1) a pedunculated cylindroma of the trachea, ensheathing the vagus nerve, 2) encephalomalacia in the region of the globus pallidus, 3) tubular degeneration of the kidneys and 4) central necrosis of the liver cords.

The abnormal alterations in the brain, liver and kidneys were regarded as the result of anoxia which accounted for the coma, jaundice and renal insufficiency manifested by the patient.

The anoxia was induced by interference with respiratory exchange consequent upon bronchospasm due to irritation of the vagus by the infiltrating cylindroma on the one hand and intermittent broncho-obstruction by the pedunculated segment of the tumor on the other. It was furthermore accentuated by the barbiturates.

The combined effect of broncho constriction and mechanical obstruction of the bronchi was responsible for the asthmatoïd and status-asthamticus like state.

#### BIBLIOGRAPHY

1. SUGGS, W. D.: *Virgin. Med. Monthly*, 70: 513, 1943.
2. RICH, A. R., AND RESNICK, W. H.: *Bull. Johns Hopkins Hosp.*, 38: 75, 1926.
3. RICH, A. R., BUMSTEAD, J. H., AND BARRON, E. S. G.: *Quoted Bull. Johns Hopkins Hospital*, 47: 6, 338, 1930.
4. HESSE, W., *Zieglers Beitr.*, 107: 173, 1942.
5. LADEWIG, P.: *Nature*, London, p. 559, 1943.
7. McIVER, M. A., AND WINTER, E. A.: *Arch. Surg.*, 46: 171, 1943.
7. BÜCHNER, F.: *Klin. Wehnschr.*, 21: 33, 751, 1942.
8. ROSIN, A.: *Beitr. z. path. Anat., u. z. allg. Path.*, 80: 662, 1928.
9. McCANCE, R. A.: *Lancet*, 2: 370, 1935.
10. BYWATERS, E. G. L., AND BEALL, D.: *Brit. M. J.*, 1: 427, 1941.
11. BEALL, D., BYWATERS, E. G. L., BELSEY, R. H. R., AND MILES, J. A. R.: *Brit. M. J.*, 1: 432, 1941.
12. MAYON-WHYTE, R., AND SOLANDT, O. M.: *Brit. M. J.*, 1: 434, 1941.
13. GLEN, A. M.: *Brit. M. J.*, 2: 875, 1941.
14. YOUNG, J., AND McMICHAEL, J.: *Brit. M. J.*, 2: 887, 1941.
15. TOMB, J. W.: *J. Trop. Med.*, 45: 125, 1942.
16. McDOWEL, R. J. S.: *Brit. M. J.*, 1: 919, 1940.



## COMPLEMENT TITRATIONS IN HUMAN SERA. II

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In earlier communications (1, 2) it was pointed out that the customary titration of complement in human and guinea-pig sera yields values which cannot be compared, since in each instance a different component of the complement limits the magnitude of the titer (3). While this conclusion remains valid, new studies (4, 5) have necessitated revisions in its interpretation.

It is now clear (5) not only that the limiting component of human complement remains C'2, or the second component, as previously indicated, but also that the titer of C'3, or third component, is not very much higher (4, 5). Study of a large number of guinea-pig sera (5) has also made it evident that in this animal the limiting component is usually C'3 and not C'1 as previously stated (3), while C'2 is generally present in only slightly greater titer than C'3.

The usual titrations of human and guinea-pig complements are therefore titrations for second and third components, respectively, and not for the second and first, as previously indicated (3, 1).

In order to titrate serum from either source for C'1, it is necessary to employ high dilutions in order to avoid anticomplementary effects, a precaution neglected in (4). The method suggested in (1) is evidently not optimal, but even so, far more extensive "fortification" of human complement was obtained than in (4). It is, however, agreed that in order to provide C'3 as well as C'2 and 4 in the titration of C'1, guinea-pig "endpiece" is preferable to "guinea-pig supernatant." However, even this may not always contain adequate amounts of C'3 and C'4, as shown elsewhere (5). Addition, as well, of heated guinea-pig serum (0.05 ml. of a 1:5 dilution) is recommended, not as the sole and inadequate reagent for "fortification" of human serum as in (4) but in combination with guinea-pig "endpiece" for titration of C'1 in human and other sera (5).

### BIBLIOGRAPHY

1. HEIDELBERGER, M.: J. Mt. Sinai Hosp., 8: 622, 1942.
2. HEIDELBERGER, M., AND MAYER, M.: J. Exper. Med., 75: 285, 1942.
3. HEGEDUS, A., AND GREINER, H.: Ztschr. f. Immunitätsforsch. u. exper. Therap., 92: 1 1938.
4. ECKER, E. E., PILLEMER, L., AND SEIFTER, S.: J. Immunol., 47: 181, 1943.
5. BIER, O. G., LEYTON, G., MAYER, M. AND HEIDELBERGER, M., In press.

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## PNEUMOTHORAX THERAPY IN CHRONIC BRONCHIECTASIS<sup>1</sup>

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In a recent study<sup>2</sup> I presented a group of cases of early bronchiectasis in which pneumothorax therapy resulted in the prompt and apparently lasting "cure" of the disease. During the past fourteen years we have employed this procedure in the treatment of thirty-five cases of chronic bronchiectasis for whom radical surgical treatment was not considered advisable for a variety of reasons. In the large majority of these cases the results of pneumothorax therapy were not satisfactory and the treatment was discontinued after a short trial. However, in some cases the outcome has been almost as gratifying as in the early cases of bronchiectasis. Because of the value of this method of therapy in these cases, and particularly because of the interest in the probable mechanism by which these results were obtained, I am prompted to make this report.

The mechanism by which pneumothorax therapy produces its favorable influence in bronchiectasis was well illustrated in the early cases referred to above. In those cases bronchiectasis developed under observation in the course of a persisting suppurative bronchopneumonia with atelectasis. The essential factor in the development of bronchiectasis in those cases was the weakening of the bronchial wall which resulted from injury to its muscular and elastic elements by infection. The physiological dilatation of the bronchi during inspiration and their elastic recoil during expiration are modified when the elasticity of the bronchial wall is impaired, so that the bronchi dilate more and retract less, with resultant bronchiectasis. This tendency to bronchial dilatation, which manifests itself even during ordinary respiration, is greatly augmented by a number of other factors which are operative in the presence of bronchopulmonary disease. These factors are: 1. cough which in reality is an exaggerated respiratory effort; 2. decreased volume of the pulmonary parenchyma (resulting from atelectasis or fibrosis of the involved lung) leading to greater than normal negative intrapleural pressure, which in turn exerts a greater pull on the bronchial wall and augments the tendency to dilatation of the injured bronchi; 3. persisting and recurring bronchopulmonary infection, with impaired drainage of bronchial secretions, prolong and enhance the progress of the bronchiectatic process.

Pneumothorax therapy tends to counteract these adverse factors. In the successful cases the induction of an optimum pneumothorax produces selective collapse and furthers rest of the involved portion of the lung thus eliminating the traumatic influence of respiration on the injured bronchi. The cough promptly decreases and disappears within one to four weeks. The highly nega-

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<sup>2</sup> In preparation.

tive intrapleural pressure is brought to an approximately normal level. The infection subsides promptly and apparently permanently, as judged by the long period of freedom from symptoms in the group of early cases previously reported. The rationale of pneumothorax therapy for chronic bronchiectasis is based on the foregoing concepts concerning the pathogenesis of bronchiectasis and on the mechanism by which pneumothorax produces its favorable effects in this condition. In chronic bronchiectasis the pathological process is more advanced and irreversible; and, in most cases, cannot be influenced by the mechanism of pneumothorax. Pneumothorax therapy has, therefore, proven of value only in a small number of cases of chronic bronchiectasis. Included in this favorable group are those cases in which the involved part of the lung is capable of retraction and thus be put at rest by the induced pneumothorax.

A short trial of pneumothorax therapy was sufficient to select the cases likely to be successful. Experience revealed that unless the clinical improvement was definite and prompt, within a few weeks after institution of therapy, delayed favorable results were no longer to be expected. Experience further disclosed that when pneumothorax was maintained despite its failure to achieve the desired degree of clinical improvement it could lead to pleural and parenchymal changes in the affected lung which would reduce the likelihood of satisfactory results by surgical intervention. For instance, in at least two of our cases the entire lung became encased in a thickened visceral pleura as a result of long continued and ineffectual pneumothorax treatment for bronchiectasis of a lower lobe. These patients eventually required pneumorectomy whereas a lobectomy would have sufficed had surgery been employed as soon as it became evident that pneumothorax was ineffective, i.e., within four to six weeks after treatment was started.

Among the cases with chronic bronchiectasis in which pneumothorax therapy proved especially effective, the following are of special interest:

#### CASE REPORTS

*Case 1*, K. N. (Adm. 321094), aged 9 years, was admitted to The Mount Sinai Hospital December 9, 1930, complaining of cough, profuse purulent expectoration, fever, night sweats and chest pain. Ten months before admission the child was taken ill manifesting symptom and signs considered to be pneumonia. She was confined to bed for two months gravely ill. Then followed a period of two months during which fever was absent, cough less severe and expectoration less profuse; the general condition had improved. Six months before admission the patient again became acutely ill with chills, fever, sweats, pain in the right chest, severe cough associated with purulent sputum up to eight ounces daily. These symptoms in varying degree of intensity were present during the following six months.

The significant findings on admission were as follows: The child appeared toxic and wasted as after a long illness. The temperature was 102°F. The trachea was displaced to the right, as were also the mediastinal structures, judging by the position of the cardiac apex. There was obvious flattening and diminished mobility of the right hemithorax. The percussion note varied between dullness and flatness over the entire right lung. The breath sounds were bronchial in quality over the upper portion of the right lung and of diminished intensity, with coarse rales and bronchi over the lower half. The left lung was normal. There was clubbing of the fingers and toes.

The hemoglobin was 63 per cent. The number of leucocytes was 18,000 with 81 per cent of polymorphonuclear cells.

A roentgenogram (fig. 1a) showed extensive involvement of the right lung with what was interpreted to be due to a suppurative bronchopneumonia with bronchiectasis, associated with chronic pleural changes. Bronchography confirmed the diagnosis of sacular bronchiectasis (fig. 1b). The mediastinum was displaced to the right. Bronchoscopy showed the right middle and lower lobe bronchi to be markedly dilated and filled with purulent non-odorous secretions which recurred after suction. The right upper lobe bronchi could not be visualized owing to marked distortion.

In view of the septic course, revealing occasional peaks of temperature elevated to 104.8°F., it was suspected that an empyema was present on the right side. A diagnostic thoracentesis was attempted in the operating room. No pus was found in the pleural cavity. This procedure, however, was sufficient to establish a large pneumothorax on the right side, so as to allow the return of the mediastinal structures to their normal central position.

To our surprise, there occurred, following this manipulation, a striking improvement in the patient's symptoms. The fever subsided and the cough and expectoration decreased

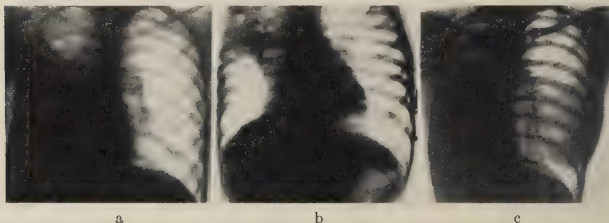


FIG. 1a: Roentgenogram of the lungs on admission, showing extensive involvement of the right lung and suspected pleural involvement. The mediastinal structures are considerably displaced to the right indicating shrinkage of the affected lung.

b: Roentgenogram of the lungs after induction of an effective pneumothorax and phrenicectomy. Note the return of the mediastinal structures to a normal position. The bronchi are partially outlined by iodized oil and show marked bronchiectasis.

c: Roentgenogram of the lungs made 10 years later. Note the marked shrinkage of the right lung with resultant displacement of the heart into the right hemithorax. The patient has remained entirely symptom-free to the present time.

almost to the vanishing point within a few days. The results were so impressive that it was decided to try to improve the situation by attempting to release the adherent right upper lobe. An operation was performed and the adhesions were separated.

This proved to be an unfortunate procedure because following the open intrapleural operation the previously established pneumothorax was largely lost and many new adhesions formed before pneumothorax refills were resumed. As a result only a limited pneumothorax could be maintained. In order to allow as much relaxation of the right lung as possible the right phrenic nerve was cut, permitting the right leaf of the diaphragm to rise considerably. After about nine months, the pneumothorax space was lost and some displacement of the mediastinal structures to the right recurred. However, the marked rise of the diaphragm which took place in the course of time was apparently sufficient to maintain adequate rest of the right lung thus favoring progressive healing.

The marked improvement in the patient's pulmonary and general condition which followed the accidental induction of a substantial pneumothorax was retarded for a while by the adverse results of the aforementioned open intrapleural operation. By the end of January 1931 the patient's temperature had receded to normal levels, and the cough and expectoration had practically disappeared. During the ensuing months and years the

child continued her improvement. She remained under observation for about thirteen years, during which period she maintained her well being and her development was normal. There has occurred marked shrinkage and fibrosis of the right lung, and bronchographic examination in 1936 showed persistence of the extensive sacular bronchiectasis in all the lobes of the right lung. However, the right chest showed little noticeable deformity.

*Comment:* In this case under discussion, the pulmonary relaxation produced by an accidental pneumothorax during diagnostic aspiration of the chest for a suspected empyema was followed by a dramatic clinical improvement. The phrenicectomy produced a progressive rise of the diaphragm which kept the affected lung at rest after the pneumothorax was gradually lost because of an obliterative pleuritis. The clinical improvement which set in so dramatically, continued during the ensuing months, and eventually resulted in a clinical cure which stood the test of many years (thirteen).

The extensive pathological changes, including universal sacular bronchiectasis of the right lung, did not preclude healing of the infection and relief of all symptoms. Although the patient has had many upper respiratory infections during these years there has occurred no lighting up of the process in the right lung, thus justifying the characterization of "clinical cure," despite the residual marked anatomical changes in the lung and bronchi (fig. 1c).

*Case 2, J. D. (Adm. 378276)*, a boy, seven years of age, was admitted to The Mount Sinai Hospital March 30, 1935, complaining of cough, profuse purulent and foul expectoration, fever and pain in the left chest.

Two years before admission the child had been subjected to a tonsillectomy under general anesthesia. During the operation two loose teeth were extracted. The day following the operation the child began to cough and his temperature rose to 104°F. Because of the persistence of these symptoms the child was returned to the hospital. Bronchoscopic examination shortly upon readmission disclosed the presence of a tooth in the left main bronchus. This was removed. Although the temperature soon subsided to normal levels, he continued to cough and expectorate 1 to 4 ounces of purulent sputum daily. After one month of hospitalization, he was sent home.

His temperature remained normal for about two weeks following his second return from the hospital. From then on and during the subsequent period of nearly two years, there were recurrent febrile episodes lasting from one to two weeks with intervals of three to four weeks during which the temperature was normal. The patient had fever for three weeks prior to his readmission to The Mount Sinai Hospital.

During the two years of his illness the cough and expectoration grew progressively worse. The sputum was purulent, gradually increased from four to six ounces a day, and eventually became foetid. Clubbing was noted during the second year of his illness.

On his third admission to the hospital the child appeared emaciated and toxic. The clinical and roentgen ray examination of the lungs indicated the presence of chronic suppurative bronchopneumonia involving the entire left lung, with extensive bronchiectasis, and marked displacement of the mediastinal structures to the left (fig. 2a).

During the early days of observation, the temperature ranged from 99°F. to 102.4°F. The hemoglobin was 72 per cent and the white blood cells numbered 17,200 on admission.

Bronchoscopy revealed a stricture of the left main bronchus at the level of the lip of the left upper lobe bronchus, which reduced the lumen to one-third of normal. Creamy pus without foul odor was seen coming from the postero-lateral branches below the stricture. The bronchi below the obstruction appeared dilated. Bronchographic examination with the aid of iodized oil disclosed extensive bronchiectasis of the left lung (fig. 2b).



Because of the gratifying results from pneumothorax therapy in case 1 it was decided to employ this procedure also in this case, since it exhibited similar features such as chronic broncho-pulmonary disease of long standing, marked mediastinal displacement toward the involved side (indicating tension on the diseased lung) and a septic course. Pneumothorax therapy was, therefore, instituted on the twelfth hospital day. As was anticipated, a high negative intrapleural pressure was encountered. About 300 cc. of air was allowed to flow in during the first treatment; and refills of about 250 cc. were made one, three, and seven days later. By that time a good pneumothorax was established although adhesions, especially about the upper lobe, prevented complete release of the left lung. With the establishment of the pneumothorax the mediastinal structures readily returned to a normal position (fig. 2b).

The object of pneumothorax therapy in this case was to place the involved left lung at maximal rest. This was accomplished by giving refills sufficient in amount and at adequate intervals to allow the mediastinal structures to remain in their normal position, and to

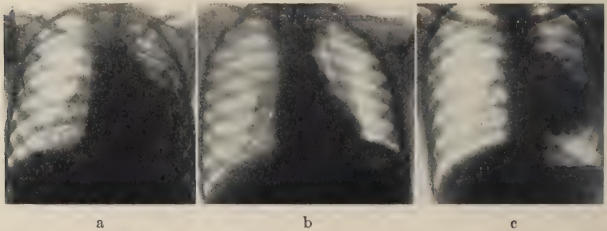


FIG. 2a: Roentgenogram of the lungs on admission, showing marked involvement of the left lung with displacement of the mediastinal structures to the left side. The appearance is most suggestive of the terminal stage of a destructive type of suppurative pneumonia associated with bronchiectasis.

b: Roentgenogram of the lungs after the induction of an effective pneumothorax and phrenicectomy. Note the marked collapse of the shrunken left lung and the return of the mediastinal structures to a normal position.

c: Roentgenogram made nine years later showing the marked residual anatomical changes in the left lung, including extensive bronchiectasis. The patient has remained symptom-free to the present time.

keep the intrapleural pressures at such levels as to have little change in the volume of the treated lung during inspiration and expiration as observed fluoroscopically.

After the second pneumothorax refill there occurred a striking improvement in the patient's clinical status. His cough and expectoration rapidly decreased, and nine days after pneumothorax therapy was started the expectoration ceased entirely. Bronchoscopic examination ten days later showed the bronchi to be free from secretion. The patient's temperature returned to normal levels, and there was no recurrence of the febrile episodes.

Because of the presence of adhesions complete rest of the involved lung could not be maintained by pneumothorax alone (as judged by fluoroscopic observation during inspiration and expiration). To improve this condition a left phrenicectomy was performed three weeks after pneumothorax therapy was started. A considerable elevation of the left diaphragm was noted three days later (fig. 2b), and this became more marked during the ensuing months. This resulted in greater rest of the involved lung and no doubt contributed substantially to the satisfactory result observed in this case.

The patient left the hospital on May 9, 1935 (about one month after treatment was instituted), entirely symptom-free and his general condition was much improved. He

continued to be treated in the Chest Clinic at The Mount Sinai Hospital at weekly, and later at longer, intervals for about two years. During this time he remained free from all pulmonary complaints. After pneumothorax therapy was discontinued and the lung was allowed to reexpand the child remained well. He has been under our observation until the present time (1944). He is now sixteen years old, is well developed, and is able to carry on normally. The left lung is considerably shrunken and shows extensive bronchiectasis (fig. 2c). The left diaphragm is still quite elevated. He has, however, no chest deformity and is able to carry on without undue dyspnoea on exertion. He has had a number of "colds" during the past nine years, but at no time did he develop a protracted cough. In brief, the clinical course in this case justifies the designation of a "clinical cure," despite the marked residual changes in the left lung.

*Comment:* The striking results achieved in these two cases followed so closely upon the institution of partial pneumothorax and phrenicectomy that a causal relationship between them cannot be denied. The mechanism involved in the development of a clinical cure in these cases is a matter for speculation. No doubt the release of tension on the involved lung and the relative rest which was produced by these procedures played the most important role in the control of the course of the disease. The fact that these patients were young children is probably another significant factor. It is a question whether similar results could be achieved in adults in whom the capacity for repairing damaged tissues and reestablishing normal function is much less marked than in the young.

In the early cases of bronchiectasis, healing of the infection in the bronchi and pulmonary parenchyma was followed by considerable anatomical restoration of these tissues as shown by the almost normal appearance of the recent roentgenograms. In the chronic cases, on the other hand, a good deal of destruction of the bronchi and of the pulmonary parenchyma took place, and repair by fibrosis resulted in marked anatomical alteration. Nevertheless, when pneumothorax, aided by phrenicectomy, was able to produce adequate relaxation of the involved lung, thus putting it at relative rest, even chronic infection of many months standing could be made to clear up and a lasting clinical cure achieved in some cases.

*Case 3, E. W. (Adm. 406, 090),* a young man, aged 22 years, was admitted to The Mount Sinai Hospital, March 22, 1937 with a history of recurring episodes of chills and fever for four years.

Four years before admission the patient experienced his first attacks of sudden chill lasting for about fifteen minutes followed by a sharp rise in temperature to 104°F. which defervessed before the end of twenty-four hours. After a day or two he felt quite well and was able to return to his usual activities.

At first these episodes of chills and fever recurred every two to three months and were of brief duration. As time went on they increased in frequency and in duration. They occurred at any time of the day or night and there was no apparent precipitating cause. During the five months before admission to the hospital they occurred almost weekly, became more prolonged and were followed by greater debility and a loss of ten pounds in weight. The last bout of chills and fever occurred one week before admission to the hospital.

The patient denied any contact with animals, did not ingest goat's milk, and he knew of no occurrence of similar manifestations among his friends. He also stated that a course of treatment with quinine had been ineffective. Examination for tuberculosis by the Health

Department yielded negative results; and, a chest film recently made was reported as normal.

The essential findings on admission were as follows:

The patient appeared chronically ill. His temperature curve was subfebrile with occasional rises to 102°F. during the first weeks of observation. He had no chills. His white blood count on admission was 23,500 with 82 per cent polymorphonuclear cells. The sedimentation rate was normal. Agglutination reactions for *b. melitensis* and *abortus* were negative. Urine, stool, and liver function tests yielded negative results. An infected tooth was removed. A left maxillary sinusitis was found and treated successfully by irrigations without any effect on the fever.

Examination of the lungs disclosed a few bronchitic rales in the left lower lobe. The patient was then closely questioned regarding pulmonary symptoms and finally admitted that he had had a slight non-productive cough for about eight years which caused him so little discomfort that he had failed to mention it on admission.

Further investigation of the pulmonary field disclosed the following significant findings: A roentgenogram revealed an irregular pneumonic process in the left lower lobe behind the heart with moderate shrinkage of the lobe. Bronchographic examination (fig. 3a) showed

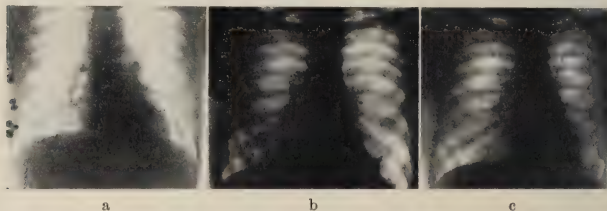


FIG. 3a: Bronchogram showing marked degree of bronchiectasis of the postero-lateral and paravertebral branches of the lower lobe.

b: Roentgenogram showing left pneumothorax with selective collapse of the left lower lobe.

c: Roentgenogram made 7 years later, showing the left lung fully re-expanded and presenting little abnormality. The patient has remained symptom-free to the present time.

a marked degree of bronchiectasis of the postero-lateral and paravertebral branches of the left lower lobe. Bronchoscopy disclosed dilatation of these bronchi, and a small amount of mucopurulent secretion was aspirated which, on culture, yielded a growth of *streptococcus viridans*.

In the absence of any other etiological factor it was concluded that the chronic bronchopulmonary disease in the left lower lobe was the most probable cause of the patient's protracted illness. It was, therefore, decided to try the effect of pneumothorax therapy.

This was started on April 12, 1937, three weeks after admission to the hospital. A pleural space was found with ease and a greater than normal negative intrapleural pressure was recorded, a common finding in the presence of atelectasis of greater or smaller extent. About 500 cc. of air was allowed to enter the left pleural cavity on each of three occasions at one day interval. By that time a very satisfactory low tension pneumothorax was established allowing complete selective collapse of the involved left lower lobe thus affording it relative rest both during inspiration and expiration (as observed fluoroscopically) (fig. 3b). One week after instituting pneumothorax therapy the patient was symptom-free and able to leave the hospital.

He was treated in the Chest Clinic at weekly and later at bi-weekly intervals for about two years. During this period he had no recurrences of the febrile episodes and remained

well otherwise. He continued to do well after pneumothorax therapy was discontinued. He has been under our observation to the present time, and has remained entirely well and able to carry on normally during the past seven years. His latest roentgenogram presents little abnormality (fig. 3c). *Comment:* In this case the pulmonary symptoms of bronchiectasis were so mild as to be overlooked by the patient and his medical attendants. The chronic infection in the involved lung and bronchi was, however, a sufficient cause for the production of recurring episodes of fever and later of other constitutional symptoms. That pneumothorax therapy could produce clearing of the bronchopulmonary infection and thus eliminate it as a source of constitutional symptoms is the important feature in this case.

*Comment:* In addition to the cases described above, pneumothorax treatment was carried out in a group of patients with limited chronic bronchiectasis in whom the chief complaint was recurring large hemoptyses. In some of these cases the cough and expectoration were only moderate in severity. Not all cases of chronic bronchiectasis with hemoptysis, however, were benefitted by pneumothorax therapy. As previously indicated, only those were likely to benefit by pneumothorax in which the affected portion of the lung was free from adhesions and could be placed at rest by the induced pneumothorax. Nor did all of the latter group benefit by this therapeutic measure. Only by a trial of pneumothorax therapy for a period of four to six weeks was it possible to select the likely successes. However, when pneumothorax proved successful in controlling an episode of hemoptysis the likelihood of a recurrence was greatly decreased. The disadvantage of this form of treatment is that it may have to be continued indefinitely. Our experience is limited with this type of case, and we have not, so far, been able to form any conclusion as to what constitutes a safe period for continuing the pneumothorax.

Obviously the ideal treatment for this or any other type of limited chronic bronchiectasis is lobectomy, provided the patient is young and well enough to stand the procedure without undue risk. The point is that in cases less suitable or entirely unsuitable for radical surgery, because of age or other disability, pneumothorax may at times offer an effective remedy.

#### SUMMARY AND CONCLUSIONS

1. The mechanism by which bronchiectasis develops in the course of suppurative bronchopneumonia with atelectasis is described.
2. The rationale of pneumothorax therapy for bronchiectasis, the manner in which it produces its favorable results, especially in early cases, is discussed in some detail.
3. Pneumothorax therapy has proven a failure in the majority of cases with chronic bronchiectasis.
4. In some cases of chronic bronchiectasis the results have been satisfactory and lasting.
  - a) Two cases are presented in which the suppurative bronchiectasis was of long standing; in which atelectasis and marked mediastinal displacement were important features; and in which the protracted clinical course (ten months and two years respectively) was characterized by repeated febrile episodes and

a septic state. These cases were promptly, and to a marked degree, benefited by pneumothorax therapy aided by phrenicectomy. The patients became symptom-free shortly after treatment was instituted, and remained well during the ensuing thirteen and nine years respectively.

b) A third case of chronic bronchiectasis in the left lower lobe is presented whose clinical course was characterized by repeated episodes of chills and fever which occurred with increasing frequency and severity over a period of four years. The establishment of an effective pneumothorax resulted in a prompt and complete recovery lasting during the succeeding seven years.

c) Reference is made to some cases of chronic bronchiectasis characterized by frequent and massive hemoptysis which were effectively controlled by the induction and maintenance of a pneumothorax, provided complete relaxation of the involved portion of the lung could be obtained. This fortunate result was not achieved in all such cases, and success or failure could not be predicted in any particular case without a trial for a period of a few weeks.

5. The ideal treatment for chronic bronchiectasis is surgical extirpation of the involved portion of the lung. In selected cases of chronic bronchiectasis, however, when radical surgical measures are too hazardous or are not feasible for one reason or another, pneumothorax may offer an effective remedy.



# A CASE OF SUBACUTE BACTERIAL ENDOCARDITIS CAUSED BY AN UNUSUAL MICROORGANISM RELATED TO THE "PLEURO-PNEUMONIA-LIKE" OR GRAHAMELLA GROUP<sup>1</sup>

C. HERSCHBERGER, D. A. DANTES, M.D., AND GREGORY SHWARTZMAN, M.D.

The majority of cases of subacute bacterial endocarditis is caused by the viridans group of *Streptococcus* (i.e. probably over 90 per cent of all cases). The remaining cases are elicited by a great variety of other microorganisms. The monograph by Libman and Friedberg (1) describes the bacteriology of the disease based on personal observations and reports in the literature. The organisms mentioned are *Neisseria*, *B. influenza*, *Spirillum surati*, *Diphtheroids*, *Brucella* group, *Nocardia* groups, including *Streptobacillus moniliformis*, *Micrococcus tetragenus*, *Staphylococcus*, various anaerobes, *Erysipelothrix*, *Doederlein bacillus*, *Bacillus necrophorus* and *Monilia*. As an introduction to the following report, the reader is referred to a more recent paper by Brown and Nunemaker (2) which embodies an excellent study of the rôle of *Streptobacillus moniliformis* in human infections with reference to bacterial endocarditis as well as to papers by Klieneberger, Klieneberger and Steabben (3), Dienes, Dienes and Edsall, Dienes and Sullivan, Dienes and Smith (4), the interesting monograph by Sabin on "pleuropneumonia-like" organisms (5); papers by Tyzzer (6) on the so-called *Grahamella* organism, the report by Stuart-Harris, Wells, Rosher, Mackie and Wilson (7) on *Hemophilus para-influenzae* and pleomorphic streptobacillus causing subacute bacterial endocarditis.

The following paper embodies a report on a case of subacute bacterial endocarditis caused by an unusual organism, which, as far as it can be ascertained, seems to be different from those previously recorded in the literature of the disease. Furthermore, the organism has not been previously seen among some 22,000 blood cultures taken in the Laboratories of The Mount Sinai Hospital during the past 19 years.

## CLINICAL REPORT OF CASE

*History:* D. K., a white man, aged 23, was admitted to the Private Pavilion of The Mount Sinai Hospital on October 31, 1943 under the care of one of us (D. A. D.) at the request of Dr. Emanuel Libman.

At the age of six a cardiac murmur was discovered. This finding was subsequently confirmed on many occasions. He was relatively well until the autumn of 1942. At that time, after a dental prophylactic treatment, he developed persistent bleeding from the gums which could not be controlled by local treatment. Repeated examinations of the blood failed to disclose evidence of anemia, thrombocytopenia, or delay in the bleeding and coagulation time. On September 13, 1942, however, the platelet count fell to 125,000 per cu. mm. and the bleeding time was four and a half minutes; the coagulation time, however, remained normal. Intermittent oozing from the gums continued throughout the course of the patient's illness.

In March, 1943, while in Miami, Fla., the patient developed what was thought to be a

<sup>1</sup> From the Division of Bacteriology, Laboratories of The Mount Sinai Hospital, New York, N. Y.

"virus pneumonia."<sup>2</sup> There was no known contact with animals at any time. Within three weeks he apparently recovered completely from the pulmonary illness. In June, 1943 he noted the presence of fever and increasing weakness. He also complained of recurring red, painful and tender spots on the finger tips. Clubbing of the fingers was noted by his physician. In August, 1943, there developed severe pain in the lower part of the right side of the abdomen, and also facial paresis. These symptoms were regarded as being due to embolization. Roentgenographic examination of the chest on August 17, 1943, revealed normal pulmonary fields. The cardiac shadow was enlarged in its transverse diameter, and the configuration indicated the presence of disease of the mitral and aortic valves. Blood cultures on August 11 and October 16, 1943, revealed no organisms.

Irregular fever and profound weakness continued and the patient was sent to New York.

*Examination:* At the time of admission to the Hospital the patient was found to be extremely weak and emaciated. There was marked pallor of the skin and mucous membranes. A white-centered petechia was present in the conjunctiva of the right lower eye lid. There was slight spontaneous bleeding from the gums which otherwise appeared normal. The lungs were clear. The heart was enlarged to the left and downward. There was a loud, rough, to and fro murmur heard over the entire precordium, being loudest just inside the apex. The spleen was palpable. There was definite clubbing of the fingers, and pitting edema of the lower extremities up to the level of the middle of the tibiae. The temperature on admission was 102°F., respirations were 28, and the pulse rate 120. The systolic blood pressure was 140 and the diastolic 80 mm. of Hg.

*Laboratory data:* The hemoglobin was 39 per cent (Sahli), the erythrocyte count was 2,150,000 per cu. mm., and the leucocyte count was 9,800 per cu. mm., of which the polymorphonuclears constituted 58 per cent, staffs 23 per cent, lymphocytes 13 per cent, monocytes 6 per cent. The urine showed a specific gravity of 1.012, a faint trace of albumin and a few erythrocytes and casts per high power field. The blood urea nitrogen was 20 mg. per 100 cc.

*Course:* It was decided to attempt to improve the patient's general condition before instituting sulfonamide therapy. Accordingly, during the first two weeks of hospitalization four transfusions (each 500 cc.) of whole blood were administered by the citrate method. The hemoglobin rose to 65 per cent. A few new petechiae appeared in the conjunctivae and in the skin of the neck. A painful, red, tender lesion occurred in the paronychium of the right middle finger; this disappeared in about 48 hours. There developed frequent rather severe pains in both sides of the chest, for which no adequate explanation was evident. Albuminuria and microscopic hematuria continued.

Despite the patient's poor condition, a massive dose of sulfadiazine (20 grams) and 40 grams of urea were given intravenously in one liter of distilled water on the 17th day of hospitalization. On the following day the blood sulfadiazine level was 15.8 and the blood urea nitrogen was 123 mg. per 100 cc. The patient was drowsy. The temperature became normal. On each of the two following days, 10 Gm. of sulfadiazine were given intravenously without urea. The temperature remained at a normal level but numerous white-centered petechiae developed. The patient was not responsive. The platelet count fell to 20,000 per cu. mm. Bleeding from the gums became more continuous.

On the 21st day the patient died suddenly. Permission for necropsy could not be obtained.

#### BACTERIOLOGY OF THE CASE

*Isolation of the organism:* Cultures of the patient's blood were made according to the following procedure used routinely in the Bacteriological Laboratories of this hospital:

<sup>2</sup> The data concerning the patient's course prior to admission was kindly supplied by Dr. S. Balofsky of Miami, Florida.

The blood specimens were obtained at the patient's bedside. Twenty-three cc. of the patient's blood were drawn from an anterior cubital vein. Fifteen cc. were divided equally among three "100 cc." Erlenmeyer flasks, the first containing veal infusion broth, pH 7.4; the second, 2 per cent dextrose-veal infusion broth, pH 7.4; and the third, 10 per cent tomato extract-veal infusion broth, pH 7.6 (8). Of the remaining 8 cc. of blood, 6 cc. were equally divided to form three pour plates: 2 cc. were mixed with each of two tubes containing 12 cc. of 2 per cent dextrose-veal infusion agar, pH 7.4; 2 cc. were mixed with a tube containing 12 cc. of plain veal infusion agar, pH 7.4, and 2 cc. were put into a tube containing 10 cc. of cooked liver broth, pH 7.4, which was sealed with 2 cc. of sterile vaseline. Samples from the flask were stained each day.

The first blood culture taken on the day following admission to this hospital revealed, after 48 hours of incubation, innumerable minute colonies of the organism, described below, in all solid media and in the flask containing 5 cc. of the patient's blood and 95 cc. of plain broth. Innumerable colonies were obtained only in solid media in a second blood culture taken five days after admission.

The organism was not found in cultures of the mouth, conjunctiva and urine.

*Morphology and staining characteristics of the organism isolated.* The recovered microorganism designated herein as #350 was invariably Gram negative, some forms remaining poorly stained. Granules appearing dark red or bluish with the Gram stain were seen consistently throughout the body of short rods and long filamentous forms (methylene blue was employed satisfactorily, Giemsa stain being preferable for demonstration of small round bodies).

The organism was markedly pleomorphic, non-motile and showed no capsules. The following forms were observed: short and long rods beaded with darkly staining granules; long filamentous forms with large darkly staining bodies adjacent to the filaments; filaments and masses of interwoven disintegrating filamentous strands with large round bodies; oval short forms with markedly tapering ends; and small granules in groups. The short rods presented a characteristic tendency to form rosettes. These consisted of rods placed side by side to form a small circle, the center of which was occupied by one or more large globoid darkly stained bodies.

Daily observations were made on the development of these various forms in serum broth for a period of 2 weeks. Following 24 hours of incubation the culture consisted of short rods arranged in rosettes. The rods became elongated in older cultures developing into filaments on the 3rd day of incubation. Long filaments predominated over other forms on the 4th and 5th days of cultivation. On the sixth day the filaments began to disintegrate and many round and globoid bodies made their appearance. About the 9th day short rods were abundant again while there were few filaments. During the remaining 90 days of observation there were seen short and pointed bacillary forms, a few filaments and numerous short rods. A series of microphotographs and electron micrographs on Plates II, III and IV illustrates the morphological appearance of the organism.

*Cultural characteristics of organism #350.* (a) *Aerobic cultivation at 37°C. in an atmosphere containing 5 per cent CO<sub>2</sub>:* No growth occurred on either plain and glucose agar or in gelatine glucose broth, plain broth and peptone water. An abundant growth was, however, obtained on human and rabbit blood agar.

After 48 hours of incubation raised, opaque and mucoid colonies with a smooth and shining surface and irregular filamentous edge were visible. The latter appeared as an underlying mat which was dry and adherent to the surface of the agar. When a block of agar containing the colonies was lightly pressed against a fresh agar surface the raised portion of the colony was easily detached, leaving on the surface of the block a dry, adherent ring with a denuded center. The ring represented the mat adhering to the agar, the denuded center being the site of the raised colony lost by contact with the fresh agar surface. Following the technique of Klieneberger (9), numerous blocks were cut out at various stages of growth, the raised colonies removed by pressing against fresh agar surfaces or dry cover slips. The denuded agar blocks were then stained with the Wayson plague stain (loc. cit. Brown and Nunemaker (2)). On examination the rings were found frequently to contain "oil" droplets, and masses consisting of some small round bodies together with larger numbers of rod-shaped and filamentous forms. No large globoid bodies were observed. It appeared that it may be possible to cultivate separately the mat forms from the opaque colonies. Observations on these cultures are under progress. The denuded surfaces of agar blocks also showed very minute single colonies adherent to the agar surface. They closely resembled the "pleuropneumonia-like" or L types seen in association with *Streptobacillus moniliformis*. For comparison of these colonies as shown on Plate I the reader is referred to Figures 1 to 5 in the paper by Sabin (5), and Figure 18 of Plate II in the paper by Brown and Nunemaker (2).

On agar containing ascitic fluid, the organism did not grow as well as on blood agar and the colonies were somewhat different. They had a dry, rough surface with an irregular and filamentous border. In stab cultures on this medium there was observed a filamentous growth studded with granules. The growth on 20 per cent serum-agar was good. The strain was readily maintained on this medium.

Loeffler medium was not liquified although growth was fairly good. No color was produced on Loeffler medium, potato and serum agar.

(b) *CO<sub>2</sub> requirements and anaerobic cultivation*: Blood agar plates receiving 0.05 cc. of a light suspension of the organism showed only moderate growth on aerobic incubation at 37°C. in the absence of CO<sub>2</sub> and significantly better growth in air containing 5 per cent CO<sub>2</sub>. Anaerobic cultures failed to grow completely in ascitic fluid, semi-solid agar, cooked liver broth, sodium thioglycollate medium and blood agar plates. The surviving organisms of the inoculum died out after 2-3 anaerobic passages.

Aerobic 20 per cent serum and 20 per cent ascitic fluid broth cultures formed a pellicle and granular strings suspended from the surface in the clear medium. There was gradually deposited a granular sediment on the bottom of the tube.

The organism failed to grow in plain meat infusion broth containing 10 per cent "Difco" yeast extract. The effect of V factor upon the growth of the organism was tested as follows:

Plain agar plates were streaked with staphylococcus and incubated for several hours. Streaks of organism #350 were then made parallel to the staphylococcus

inoculations. No growth of the organism was obtained in the presence or absence of CO<sub>2</sub>.

(c) *Optimum temperature for cultivation, thermal death point and duration of survival in cultures:* No growth occurred at room temperature, 37°C. being most favorable for cultivation of the organism.

Serum broth cultures were tested for viability after storing for various periods of time at different temperatures. The organism remained viable after 135 days of incubation at 37°C. under CO<sub>2</sub>. Longer incubation periods were not tested. The cultures died out after maintenance for 102 and 107 days at room temperature and in the refrigerator, respectively.

The thermal death point was determined by immersing into a water bath sealed capillary tubes containing samples of a 48-hour-old serum broth culture of the organism. The culture was completely killed by exposure to 52°C. for 20 minutes. After 10 minutes at this temperature there was partial destruction since the organism grew out scantily in subculture on blood agar on the 4th day of cultivation. At temperatures of 51°C. and lower for 30 minutes, the organism was not destroyed.

*Biochemical tests.* The organism produced a catalase. Methylene blue (1 drop of 10 per cent aqueous solution) was reduced within one hour as actively as in the presence of *E. coli*. The indol test was positive. No lead acetate was present. Nitrates were not reduced to nitrites. Acidification of litmus milk began on the 7th day, becoming complete on the 11th day of incubation. There was no coagulation of milk. Bile failed to dissolve the organism. There was no hemolysis of red blood cells in solid and fluid media. After several days of growth on blood agar there may appear from time to time a small zone of methemoglobin.

Tests for fermentation of sugars were made in serum containing semi-solid agar media. There was no fermentation of glucose, while there was obtained slight acidification without gas of saccharose, maltose, mannite and lactose.

*Animal tests.* The organism was non-pathogenic to mice, guinea pigs and rabbits, following subcutaneous, intravenous and intraperitoneal injections. The organism was not recovered from mice killed 1-16 days following intravenous and intraperitoneal injection of the suspension.

*Serological tests. Methods and materials:* Agglutination tests with organism #350 were carried out with saline suspensions of live cultures grown on blood agar plates and a formalinized antigen. The antigen was prepared in the following manner:

Rabbit serum broth cultures were centrifuged until the supernate became clear. The sediment was washed in saline by repeated centrifugalization. Formalin in the final concentration of 0.1 per cent was added to the saline suspension of the sediment. The suspension was placed into a glass-stoppered bottle and stored in the refrigerator. Three days later the glass stopper was replaced by a cotton plug and left in the refrigerator for 3 more days. On expiration of this period of time the suspension was sterile.



*Sera employed.* Serum 310 was obtained from a rabbit immunized with a washed suspension of live organisms #350 grown on blood agar. Injections were made intravenously for five consecutive days in doses of 0.1, 0.2, 0.4 and 0.5 cc., respectively. The animal was bled 7 days after the last injection. In addition there were used the *anti-Streptobacillus moniliformis* serum, kindly supplied by Doctor F. Parker, Jr. and the *Fothergill anti-H. influenzae* horse serum. The diagnostic *Types A and B rabbit sera* of E. R. Squibb and Sons were employed for the "Quellung" tests as follows: One cc. of a heavy suspension of organism #350 was injected into the peritoneum of a mouse. Four hours later the mouse was killed and the peritoneum was washed with saline. Two drops of the peritoneal washing containing the organisms were placed on a slide and methylene blue added to each drop. The contents of one capillary tube containing A and B sera were mixed with the suspensions

TABLE I  
*Results of agglutination tests with various antigens*

| IMMUNE SERA   | LIVE SUSPENSION OF #350 AND FORMALINIZED ANTIGEN #350 | H. INFLUENZAE TYPE B | H. INFLUENZAE HEMOLYTICUS MENINGITIS STRAIN* | H. INFLUENZAE "RESPIRATORY" STRAIN† | H. INFLUENZAE TYPE A |
|---|---|----------------------|--|-------------------------------------|----------------------|
| Serum #310 rabbit immunized with organism #350              | 1:512   | neg.                 | neg.   | neg.                                | —                    |
| Anti-Streptobacillus moniliformis serum (Parker)            | neg.  | —                    | —  | —                                   | —                    |
| Fothergill anti-H. influenzae serum (horse)                 | neg.  | 1:32                 | 1:16   | 1:128                               | —                    |
| Rabbit anti-H. influenzae Type A serum                      | no "Quellung"   | no "Quellung"        | no "Quellung"                                | no "Quellung"                       | "Quellung" 1:10      |
| Rabbit anti-H. influenzae Type B serum                      | no "Quellung"   | no "Quellung"        | no "Quellung"                                | no "Quellung"                       | no "Quellung"        |
| Patient's serum   | 1:128   | neg.                 | neg.   | —                                   | neg.                 |
| 10 sera from patients suffering from non-bacterial diseases | neg.  | —                    | —  | —                                   | —                    |

\* This strain shows hemolysis on blood agar and requires the V factor for its growth.

† This strain produces no hemolysis and fails to grow in the absence of the X factor.

— = not tested.

on the slide. The mixtures were examined microscopically under cover slips immediately, and 15 and 30 minutes later for capsular swelling.

Agglutination tests were read after 3 hours of incubation in a water bath at 37°C. and again after storing in the refrigerator overnight.

As may be seen from Table I, clear-cut agglutination of organism #350 was obtained with the patient's serum, while 10 sera from other patients failed to give the reaction. This finding indicates the etiological significance of the organism in the case reported. Cross agglutination tests aided in differentiation of organism #350 from *H. influenzae* and *Streptobacillus moniliformis* and *Brucella*.

*Differentiation of organism #350 from allied microorganisms.* In view of the extreme pleomorphism of the organism described, it becomes necessary to point

out its differentiation from a great variety of Gram-negative organisms with which there is some morphological similarity, especially those previously found in cases of subacute bacterial endocarditis.

*Differentiation from Bacteroides and Bacteroides-like organisms.* The strict aerobiosis of the organism clearly differentiates it from strictly anaerobic organisms of the genus of *Bacteroides* and *Bacteroides*-like organisms of Prevot, i.e. *Ristella capsularis*, *Spherophorus* (including actinomyces or *Bacillus necrophorus*), *Spheroillus*, and the genus of *Fusobacterium* represented by the well-known *Fusobacterium plauti-vincenti*. The difference is sufficiently clear-cut to make superfluous the description of other differentiating cultural and biochemical characteristics.

*Differentiation from Brucella and Pfeifferella mallei and Pasteurella groups.* The morphological appearance and lack of serological relationship by clearly negative cross-agglutinations unequivocally differentiate organism #350 from the *Brucella*. The biochemical, morphological, cultural and especially pathogenic properties of the *Pfeifferella* and *Pasteurella* groups differ so markedly from those of organism #350 that no detailed consideration is required.

*Differentiation of organism #350 from Genus Hemophilus.* Inasmuch as Genus *Hemophilus*, represented by *H. influenzae* and para-*influenzae*, is a pleomorphic, sometimes filamentous, aerobic, Gram-negative organism, differentiation from the organism described requires special attention. The differences are as follows:

Organism #350 is differentiated from this genus by its ability to grow in the absence of hemoglobin (i.e. X factor) and its failure to grow on plain broth in the presence of the staphylococcus V factor (page 298) and yeast extract. Most of the strains of *hemophilus* require the presence of X and V factors, while some may grow in the presence of one or another factor alone. Furthermore, differentiation from various strains, which would be too lengthy for description, is made on the lack of ability of the organism described to produce nitrites from nitrates; non-pathogenicity for mice; lack of hemolysis; the type of growth in fluid medium; lack of pigment formation on potato; and in lack of serological relationship. Some features in common, such as indol and catalase production, fail to indicate any relation to the *Hemophilus* genus, inasmuch as the strains of *hemophilus* showing this characteristic differ in many other respects from the organism described. Differentiation of organism #350 from the organism isolated from cases of subacute bacterial endocarditis by Stuart-Harris, Wells, Rosher, Mackie and Wilson are of particular interest here. The organisms recorded by the authors were identified as para-influenza and streptobacilli. The morphology of these is quite distinct from that of organism #350. They are very small and coccobacillary in shape, showing but little irregularity in form or staining and presenting no characteristic arrangement. The colonies are also distinct, being translucent and apparently having no mat as seen in the colonies of the #350 organism. The following features were also different from those described in connection with organism #350. The V factor was essential for the growth of three strains. None of the strains produced indol, or had any effect

on litmus milk. Catalase production was poor or absent and the strains were facultative anaerobes, although growing better aerobically. The addition of blood and serum did not have a marked effect on growth.

Similarly to the strains of "parainfluenza" described by Stuart-Harris, Wells, Rosher, Mackie and Wilson, organism #350 produced acid in glucose, maltose and sucrose; improved growth was obtained on addition of CO<sub>2</sub> to the atmosphere. Broth cultures contained a flocculo-granular deposit. There was no pathogenicity for laboratory animals. However, all the points of dissimilarity between #350 and parainfluenza were sufficiently significant and numerous to permit a differentiation of this organism from the strains described by the authors just mentioned.

*Differentiation of organism #350 from Streptobacillus moniliformis and its possible relation to pleuropneumonia-like forms.* The groups of *Streptobacillus moniliformis* widely spread among rodents are yet inadequately characterized; the best studied are those members which elicit human infections. Furthermore, the cultural, biochemical and serological properties known thus far are not sufficiently specific to enable clear-cut definition. The morphological appearance offers possibly the best criteria for identification, this, however, being complicated by the existence of so-called L forms, or pleuropneumonia-like organisms which may be either symbionts or variants of the *Streptobacillus moniliformis*. Organism #350 described in this paper is morphologically clearly distinct from *Streptobacillus moniliformis*, omitting for the moment the L form from consideration. Thus, according to the description of Brown and Nunemaker, *Streptobacillus moniliformis* possesses the following morphological features:

There are observed long filaments which may form irregular numbers of large or small spindle-shaped swellings packed with fine granules. Furthermore, filaments show a distinct tendency to fragment in dot-dash fashion (Morse code) and form along the course of fragmented filaments large round bodies. Organism #350 shows no fragmentation. As may be seen in the electron microscope photographs (Plate IV), the space between sections of filaments are connected by thin strands of the matrix. Furthermore, single or resting bodies are young forms of the rods or filaments. They too show granules embedded in a matrix. As the body forms into rod, and rod into filament, the number of granules in the matrix increases proportionately.

However, while organism #350 is definitely distinct from *Streptobacillus moniliformis*, it shows a tendency to undergo certain changes which may indicate the presence of symbionts or variants. These forms are related to the L forms of "pleuropneumonia-like" organisms. The features pointing to the relationship are as follows:

After 2 to 3 days of incubation the surface of the colony can be easily detached leaving a mat which is dry and embedded in the mass of media. This detachment occurs when a coverslip is placed over a colony to make an impression preparation. The colony detached may contain vacuolated areas with some peculiar chemical substance staining brown with Giemsa, with the organism discernible on its surface or around the material. Furthermore, the older cultures clearly

show a transformation of the rods and filaments into exceedingly small forms, seemingly consisting only of granules under the optical microscope. On the other hand, the above peculiar forms do not show the extraordinary pleomorphism seen in pleuropneumonia organisms, and the L forms of rats (Klieneberger, Dienes and Smith, Brown and Nunemaker) and mice (Sabin). There are, however, certain suggestive similarities, namely, the appearance of some microscopic colonies seen after the removal of the large elevated colonies, low thermal death point, appearance of growth in fluid media, the strict requirement for high protein contents of media, etc.

*Comparison of organism #350 with Grahamella.* Tyzzer described an interesting group of organisms, the so-called Grahamellae occurring in the blood of rodents, responsible for acute and latent infections. The features described in the opinion of the author do not disclose any distinct differentiation of this group from the *Streptobacillus moniliformis* group. Nevertheless, the morphological characteristics definitely separate the organism from the typical strains of *Streptobacillus moniliformis* of rat-bite fever, especially those transmitted to man (i.e. absence of fragmentation and nodular thickenings). Judging from Tyzzer's description there may exist certain points of similarity between the Grahamellae and organism #350, namely: long survival time at room temperature; the existence of unbranched beaded rods with some globoid forms; compact masses of granules and globoid forms resembling resting stages; and abundant growth on blood media.

#### DISCUSSION

The organism described in this paper may be differentiated with certainty from *H. influenzae*, *Streptobacillus moniliformis* of rat-bite fever, *Pfeifferella mallei*, *Pasteurella*, *Brucella*, *Bacteroides* and *Bacteroides*-like organisms. It seems to be somewhat similar to Grahamellae of Tyzzer. In addition certain features indicate that the organism may be associated with the L forms similar in some respects to those described by Klieneberger, or be related to a pleuropneumonia-like organism. The final identification of the organism described must remain unsolved for the following reasons:

(1) The exact nature of the pleuropneumonia-like organisms is still uncertain, since they may be symbionts or merely variants of other organisms (Klieneberger, Dienes, Smith, Brown and Nunemaker).

(2) The possibility that L forms may be also associated with Grahamellae is not excluded.

(3) Our knowledge of pleuropneumonia category of organisms is not sufficiently advanced to determine whether the absence of certain forms in organism #350 necessarily precludes its acceptance as a representative member of the group.

It may be advisable to refrain from the final identification of this organism by defining it as one of human origin bearing resemblance to the Grahamellae and possibly associated with a variant or symbiont which possesses some characteristics in common with the L forms.

The finding of this organism is of interest for several reasons:

- (1) Its occurrence in man is exceedingly rare.
- (2) The organism may be easily overlooked in view of the small size of colonies in "pour plates," staining characteristics, bizarre forms, requirement of high protein content on media and of addition of CO<sub>2</sub> to the atmosphere.
- (3) The finding of this organism in our case does not necessarily imply its exogenous virulence for man inasmuch as the infection occurred on heart valves apparently rendered susceptible by rheumatic heart disease. Nevertheless, the bacteria to which organism #350 is related show interesting pathogenic effects upon animals, resembling some obscure human infections (joint and heart lesions, etc.). The possibility that a member of this or these groups may also propagate in man suggests that it is necessary to search with care for similar organisms in the human bacteriological material.

#### SUMMARY

An unusual organism was found in a case of subacute bacterial endocarditis. This organism is somewhat related to the *Grahamella* group and may be associated with a pleuropneumonia-like or so-called "L" symbiont or variant. The differentiation from allied microorganisms is described in detail.

The authors are thankful to Miss Helen Data for capable assistance.

#### BIBLIOGRAPHY

- (1) LIBMAN, E., AND FRIEDBERG, C. K.: "Subacute Bacterial Endocarditis," edited by H. A. Christian, reprinted from Oxford Loose-Leaf Medicine, Oxford University Press, Inc., New York, 1941.
- (2) BROWN, T. MCP., AND NUNEMAKER, J. C.: Bull. Johns Hopkins Hosp., 70: 201, 1944.
- (3) KLIENEBERGER, E.: J. Path. Bact., 39: 409, 1934; 40: 93, 1935; 42: 587, 1936. J. Hyg., 38: 458, 1938; 39: 260, 1939; 40: 204, 1940.  
——— AND STEABEN, D. B.: J. Hyg., 37: 143, 1937.
- (4) DIENES, L.: Proc. Soc. Exper. Biol. & Med., 42: 636 and 773, 1939.  
J. Bact., 44: 37, 1942. J. Infect. Dis., 65: 24, 1939.  
——— AND EDSALL, G.: Proc. Soc. Exper. Biol. & Med., 36: 740, 1937.  
——— AND SULLIVAN, E. R.: Proc. Soc. Exper. Biol. & Med., 41: 424, 1939.  
——— AND SMITH, W. E.: Proc. Soc. Exper. Biol. & Med., 51: 297, 1942.  
———: J. Bact., 48: 125, 1944.
- (5) SABIN, A.: Bact. Rev., 5: 1, 1941.
- (6) TYZZER, E. E.: Am. Philosophical Soc., 85: 359, 1942.
- (7) STUART-HARRIS, C. H., WELLS, A. Q., ROSHER, A. B., MACKIE, F. P., AND WILSON, G. S.: J. Path. & Bact., 41: 407, 1935.
- (8) SHWARTZMAN, G., AND GOLDMAN, J. L.: Arch. Surg., 34: 82, 1937.
- (9) KLIENEBERGER, E.: J. Path. & Bact., 40: 93, 1935.



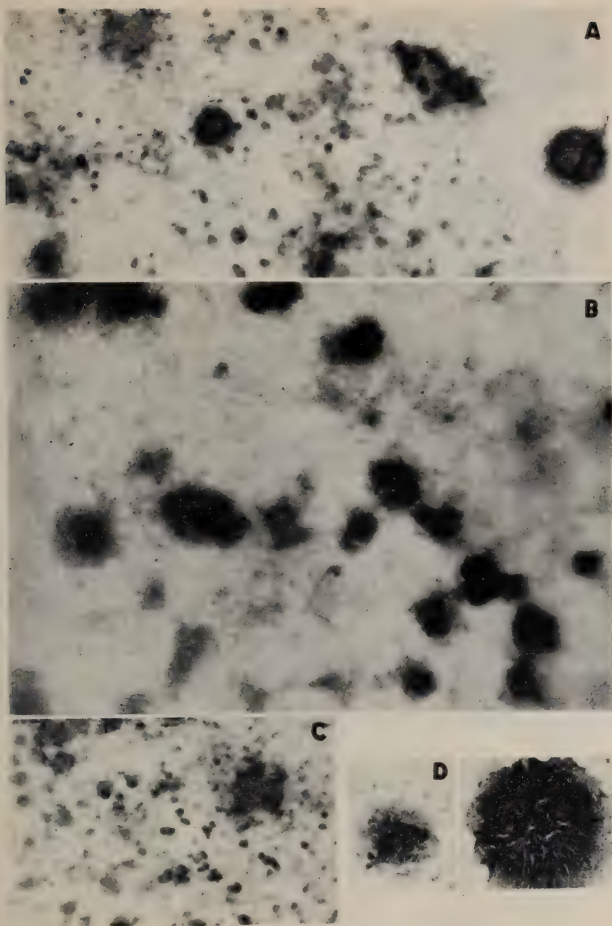
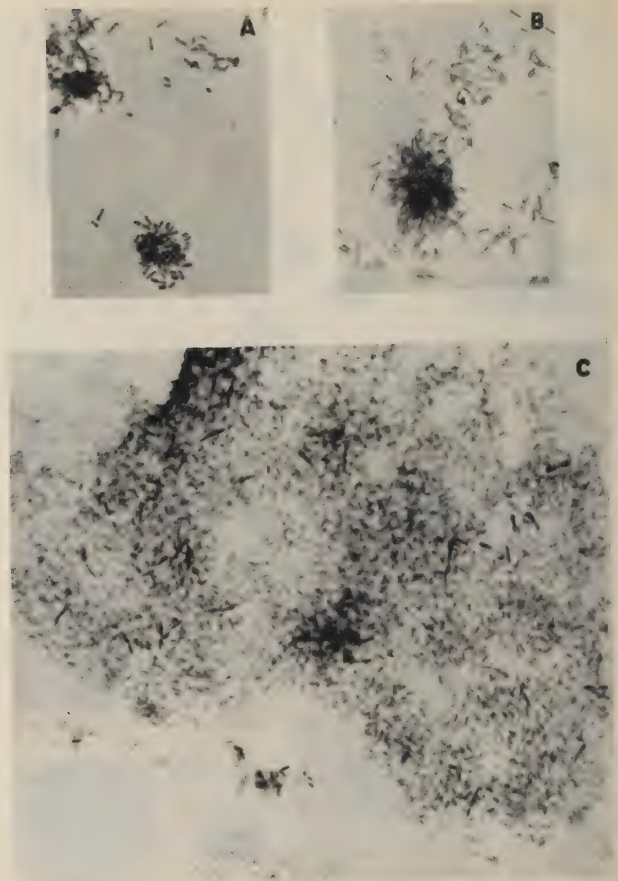


PLATE I

SECTIONS OF AGAR BLOCKS. WAYSON STAIN. 150 X

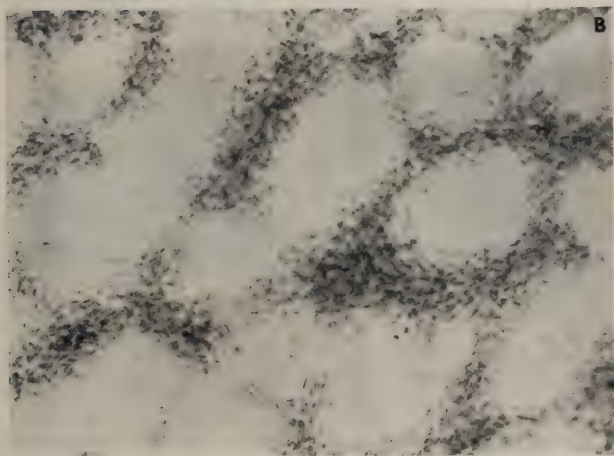
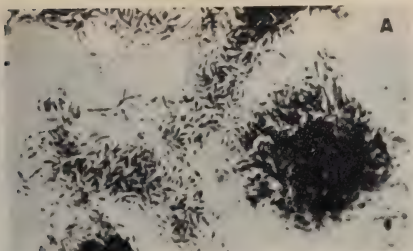
The colonies shown in this plate were adherent to the agar and were found under a film of surface growth. The surface growth, not shown here, was removed by contact with a fresh agar surface. (A), (B) and (C): 3-day old cultures; (D) and (E): 4-week old cultures.



## PLATE II

IMPRESSION PREPARATION. GIEMSA STAIN. 1800 X

Age of cultures: (A) 17 hours; (B) 3 days; (C) 7 days. Note the appearance of "rosettes" described in the text.



## PLATE III

(A) SECTION OF AN AGAR BLOCK. WAYSON STAIN

Age of culture 21 days

(B) IMPRESSION PREPARATION OF A 7-DAY OLD CULTURE

Upon impressing the cover slip on the surface of the agar, the central portion of the colonies adherent to the agar failed to appear on the cover slip. The peripheral zones of growth in the illustration represent the "mats" described in the text.

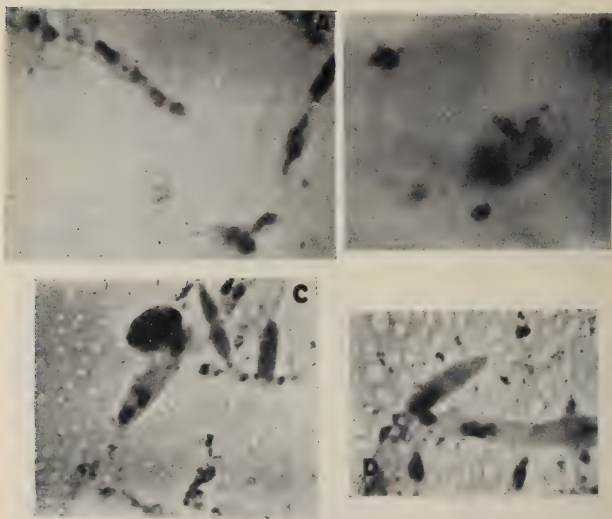


PLATE IV

## ELECTRON MICROGRAPHS

(A) Human serum broth culture. 24 hours old. Granular deposit in the culture placed on the screen. The screen was washed 3 times with distilled water. 5250  $\times$ .

(B) Colonies of a 12-day old blood plate culture were emulsified in Locke solution. A drop of the emulsion was placed on a screen. The screen was washed 3 times in distilled water. 10,500  $\times$ .

(C) Preparation of a 24-hour old human serum broth culture. The centrifuged sediment was suspended in broth diluted with Ringer solution, 5250  $\times$ .

(D) Preparation of a 24-hour old human serum broth culture. The centrifuged sediment was suspended in broth diluted with Ringer solution. 5250  $\times$ . Note dense structures embedded in the matrix and globoid bodies in (B) and (C). The high magnification of globoid body in (B) demonstrates a structure similar to that observed in bacillary forms, i.e. dense bodies embedded in the matrix.

## VENOUS PRESSURE CURVES IN NORMAL AND ABNORMAL CIRCULATORY STATES. I. NORMAL VENOUS PRESSURE CURVES AND THE NEGATIVE "HEPATO-JUGULAR REFLUX PHENOMENON"<sup>1</sup>

WILLIAM M. HITZIG, M.D.

The study of the veins, which according to Lewis (1), still suffers an egregious neglect, dates back to Stephen Hales (2). In 1769 Hales measured venous pressure in the horse and sheep by inserting a glass tube into the jugular vein and observing the blood column, a direct method still in use today. Although systemic venous engorgement has long been associated with a failing heart, the quantitative registration of venous pressure in circulatory diseases received its impetus from the work of Starling (3), Henderson (4) and others who first recognized the significance of the venous return to the heart in the regulation of the circulation. Since then, and particularly during the past decade, venous pressure measurements have been employed not only by the investigator in the elucidation of fundamental circulatory mechanisms, but also by the clinician in the bedside recognition and therapeutic management of circulatory syndromes. Excellent reviews on this subject are given by Eyster (5), Villaret, Saint Girons and Justin-Besancon (6), Pogany (7), Fishberg (8) and others.

The absolute height of the venous pressure as measured in an antecubital vein, as is well known, serves as a rough index of the systemic venous return and of the ability of the right heart to cope with it while at rest. Values within certain limits represent a normally functioning right ventricle. Marked depression of the venous pressure usually signifies a diminished venous return, as found in peripheral failure or shock, and a numerical elevation of the systemic venous pressure is regarded as the cardinal sign of right heart failure. However, unless clinical or other laboratory methods are invoked, incipient or lesser disturbances of right ventricular function may frequently remain unrecognized, because in such cases the initial pressure in the veins may still be within the upper limits of normal. In view of this, it may therefore be stated that isolated "static" measurements of venous pressure in systemic veins are not entirely adequate, since such measurements performed *at rest* may fail to shed sufficient light on the functional reserve of the right heart.

The inadequacy of the "static" measurements of venous pressure also becomes apparent in occasional cases of frank right heart failure where despite the persistence of the classical clinical manifestations of right ventricular insufficiency, normal or nearly normal initial venous pressures may be encountered at rest. This is especially true in incipient right heart failure, as well as in markedly advanced cases whose treatment with diuretics and digitalis has altered significantly the ratio between the circulating blood volume and the total venous capacity. In such cases only "dynamic" measurements of the venous pressure obtained by increasing the venous return either through exercise or through

<sup>1</sup> From the 2nd Medical Service of Dr. Isidore Snapper, The Mount Sinai Hospital, New York, N. Y.



rapid intravenous fluid administration can confirm in a physiological way the presence of lesser or greater disturbances of the functional reserve of the right heart.

The functional reserve of the right heart is, roughly speaking, directly proportional to its capacity to cope with an increased venous return. This explains the absence of a cardiac reserve in patients with frank right heart failure during exercise or during rapid intravenous fluid administration. In such instances the increased venous return engendered by effort or rapid venoclysis is accompanied by an increased elevation of the systemic venous pressure as well as by exaggeration of the clinical symptoms. Such physiologic measures can be employed in a similar though less striking manner to unfold the presence of only slight weakness of the right ventricle. Although in these borderline cases the right heart is still able to handle the venous return *at rest* and maintain the systemic venous pressure at a normal level, augmentation of the venous return may serve as the sole means of bringing to the surface the earliest evidence of impairment of right ventricular function.

The circulatory disturbance which characterizes the inefficient right ventricle is best understood in the light of Starling's fundamental *law of the heart*. The normal heart maintains a constant venous pressure level during exercise or during rapid fluid administration provided that the augmented venous return does not exceed its functional capacity. Unless exercise is too vigorous or the quantity of the intravenous fluid introduced in a unit of time is too high, the normal heart accommodates itself to the increased return by means of the following two mechanisms: 1) increased diastolic filling with resulting increase in the output per stroke, and 2) increased rate, which if present probably arises from the increased pressure in the great veins and heart (Bainbridge reflex). In the insufficient right heart, on the other hand, these mechanisms operate less effectively. The decrease in output of the right ventricle preponderates over the compensatory tachycardia with consequent accumulation of blood in the systemic veins and elevation of the venous pressure.

"Dynamic" methods for measuring the venous pressure following exercise and intravenous fluid administration have been carried out in selected cases but have not been accepted for routine use. The results do not justify the effort in view of the technical difficulties and untoward physiologic disturbances occasionally encountered in cardiac patients.

During the past ten years the author has employed a satisfactory clinical method for recording in a dynamic way the ability of the right heart to cope with an increased venous return. The procedure, a simple adaptation of the principles enunciated above, is carried out at rest and embodies a phenomenon first described by Pasteur (9) and later elaborated on by Rondot (10), who found that manual compression of an engorged liver causes swelling of the veins of the neck. Pasteur regarded it as a phenomenon associated with tricuspid regurgitation, but Rondot, who realized its broader implication, correctly attributed it to weakness of the right ventricle and gave it the name of *hepato-jugular reflux*. Later, Plesch (11) also applied this sign to clinical cardi-

ology and concluded that its presence indicated right ventricular insufficiency. Hitherto, observation on the fullness of the cervical veins during this maneuver has been confined solely to cases in which there was frank failure of the right side of the heart. Similar observations on the state of the cervical veins in "normals" and in lesser grades of right ventricular insufficiency have not been previously mentioned except briefly by the author (12), who applied and confirmed the value of this phenomenon in a large series of normal and abnormal circulatory states. Even without actually measuring the venous pressure, the functional efficiency of the right ventricle was readily ascertained at the bedside by inspecting and by palpating the resistance of the superficial cervical veins during combined right upper abdominal compression and deep breathing.

The maneuver is carried out as follows: The recumbent patient is told to relax and breathe regularly and deeply. He may be required to turn his head slightly to render his neck veins more prominent. During these respiratory excursions the observer, while inspecting and palpating the superficial cervical veins, applies gradually increasing pressure over the right upper abdomen with the palmar aspect of his outstretched hand and records the effect of deep breathing (especially inspiration) upon the vein he has selected. Observation of the veins in a wide variety of carefully observed cases during a period of ten years permits the following generalizations with regard to the functional status of the right ventricle:

- 1) If right upper abdominal compression causes visible collapse or emptying of the superficial cervical veins (external jugular vein) during deep breathing, it invariably indicates a normally functioning right ventricle *at rest*.

- 2) If right upper abdominal compression does not cause any noticeable change in the superficial cervical veins (external jugular vein) during deep breathing, and palpation reveals prominent but soft "inelastic" veins (over-distended or gaping veins, as seen in long standing bronchitis or emphysema), it also invariably indicates a normally functioning right ventricle *at rest*.

- 3) If right upper abdominal compression causes the superficial cervical veins (external jugular veins) to become either visibly fuller or palpably more tense during deep breathing, it invariably indicates an insufficient or decompensated right ventricle *at rest*, the degree of "congestive" failure being directly proportional to the resistant fullness or tension of the cervical veins.

This procedure, if correctly applied can offer inestimable aid in clinical cardiology. For example, it can be of definite value at the bedside for the prompt recognition of extra-cardiac causes of hepatomegaly, ascites, peripheral edema and other symptoms that may mimic congestive failure. On the basis of a large series of well-controlled cases it has actually become axiomatic to regard an absent Pasteur-Rondot (hepato-jugular reflux) phenomenon as proof *par excellence* that the symptoms enumerated above do not owe their origin to a failing heart. In several instances the technical application of this phenomenon and the understanding of its clinical implications has facilitated in a unique way the management of cardiac patients who were unable to avail themselves of adequate medical care. Thus, the hydraemia of chronically recurring congestive failure was suc-

cessfully controlled by patients' families who after a period of coaching were able to recognize that a positive Pasteur-Rondot phenomenon was a signal for prompt administration or intensification of routine cardiac measures. Because of certain compelling circumstances, one such patient with arteriosclerotic heart disease, auricular fibrillation and generalized anasarca was maintained in a fair state of compensation for several years by a member of his family, whose knowledge of the significance of this phenomenon served as a guide for more intensive digitalization, fluid restriction and mercurial diuresis.

The foregoing observations on the veins were correlated with actual measurements of the height of the venous pressure in one of the tributaries of the superior vena cava (antecubital or external jugular veins) before and during one minute of sustained right upper abdominal compression. It was found that when the venous return was temporarily increased by means of abdominal compression, the resulting height of the venous pressure as measured in the arm or neck veins reflected more accurately the functional status of the right ventricle.

The application of the hepato-jugular reflux phenomenon to manometric measurements of the venous pressure has yielded characteristic venous pressure curves for normal and abnormal circulatory states. The results obtained in "normals" form the basis of this paper. The venous pressure curves in abnormal circulatory states will be presented in a subsequent publication.

A close correlation existed between the manometric findings and the observed state of fullness of the veins of the neck. Occasionally, discrepancies occurred and when they did, the clinical course corroborated the greater accuracy of the manometric method. This was especially true of borderline or so-called "incipient" right heart failure cases, where a manometric rise of from 2 to 5 cm. during right upper abdominal compression not infrequently escaped clinical detection. On the basis of the foregoing observations, it may be concluded that the manometric method is superior to clinical observation of the status of the cervical veins (presence or absence of hepato-jugular reflux phenomenon) for the following reasons:

- 1) It makes possible relatively accurate quantitative data for comparative observations. (The determination of the venous pressure curve can be repeatedly carried out at the bedside without significant injury to the veins).

- 2) It permits more accurate differentiation of extra-cardiac from true cardiac conditions, especially in doubtful cases where the mimicry is confusing or the initial venous pressure is high normal or even above normal.

- 3) It permits the detection of lesser grades of right heart failure not grossly demonstrable in the veins of the neck since it is often difficult to judge on clinical grounds alone the presence of increased distention of the external jugular veins unless there is manifest failure of the right side of the heart. This is particularly true in patients whose external jugular veins are hidden by a thick panniculus, or whose veins are excessively prominent or gaping either congenitally or as a result of phlebosclerosis or other degenerative changes.

- 4) It permits the recording of a fall of venous pressure—an interesting finding encountered only in normal individuals—imparting thereby the essential character to the normal venous pressure curve.

## CLINICAL MATERIAL

More than 2,000<sup>2</sup> adult ambulatory and hospital patients from the out-patient and ward services of The Mount Sinai Hospital were observed during the past 8 years. These patients suffered from a variety of circulatory and non-circulatory conditions. In addition, a group of 45 normal ambulatory young men (residents of the Fred Lavanburg Home) between the ages of 16 and 24 were also studied.

## METHODS

Venous pressure curves (initial venous pressure and height of venous column when the venous return was temporarily increased) were obtained in all patients. Circulation times with ether (13) and saccharin (14) or decholin (15) were also performed on the great majority of patients.

## VENOUS PRESSURE CURVES

Venous pressure curves were obtained by recording the initial venous pressure in one of the tributaries of the superior vena cava (antecubital or external jugular veins) by the direct methods of Taylor, Thomas and Schleiter (16), and Moritz-Tabora (17). After these readings were recorded, the rise or fall of the venous column in the manometer tube was determined by temporarily increasing the venous return to the heart by means of the following maneuvers:

A) right upper abdominal compression for about one minute

<sup>3</sup>B) left lower abdominal compression for about one minute, or

<sup>3</sup>C) passive elevation of the lower extremities to a plane perpendicular to the body for about one minute.

*I. The measurement of the initial venous pressure*

a) *The Taylor, Thomas and Schleiter method.* The method was modified slightly by moistening the inside of the sterile "L" shaped tube with 10-30 per cent solution of sodium citrate as an anti-coagulant. In this way the sensitivity of the manometric system was maintained and protracted measurements were made possible. The subject was prepared for the venous pressure measurements as follows: He reclined and was encouraged to relax after a large antecubital vein had been selected. His arm was supported on a pillow so that the antecubital surface was at a level 5 cm. beneath the anterior chest wall at the insertion of the fourth rib (the zero point). Theoretically, the zero point corresponded to the assumed level of the caval openings in the right auricle (a point much disputed by other investigators). A tourniquet, or preferably a loose blood pressure cuff was applied around the arm and inflated to about 40 to 60 mm. of mercury. The skin was cleansed with alcohol. A 16 to 18 gauge needle was attached to the manom-

<sup>2</sup> The bulk of these observations is based on studies made on the Second Medical Service during the period it was under the direction of Dr. B. S. Oppenheimer and Dr. Eli Moschowitz. Some of the material included in this investigation is from the First Medical Service of Dr. George Baehr.

<sup>3</sup> Because the results of maneuver B paralleled in a general way those obtained in maneuver A, and because maneuver C also presented technical difficulties, both of these maneuvers (B and C) were eventually abandoned.

eter and inserted into the vein. At this point it is important to emphasize the following precautions to insure successful measurements:

- 1) The patient must rest for at least 8 to 10 minutes before the measurement is taken. The patient must be relaxed throughout the procedure. It is important to test this while readings are taken. This can be done periodically by passively flexing the elbow. If the patient is not relaxed, the muscles of his upper extremity are tense and passive flexion of the elbow will be met with resistance.

- 2) A large antecubital vein must be selected, because a larger vein yields more accurate readings.

- 3) A 16 to 18 gauge needle must be employed because the sensitivity of the manometric system is dependent largely upon the bore of the needle. Furthermore, the larger the bore the less the incidence of clotting within the manometer. In subjects who are hypersensitive to pain or when using a large gauge needle it is advisable to infiltrate the skin overlying the vein with novocaine. This enhances relaxation—especially when an external jugular vein is employed.

- 4) The arm must not be internally rotated nor excessively abducted to avoid interference with the venous return. If a neck vein is employed, excessive rotation of the head must also be avoided for similar reasons.

- 5) The beveled edge of the needle must lie freely within the vein and not impinge against its walls.

After the blood rose in the manometer the tourniquet or blood pressure cuff was released. When the blood column reached a stationary level the reading was recorded. This represented the *initial venous pressure* by the "blood-up" method. The arm was then again compressed. The prompt rise of the blood column in the manometer confirmed the patency of the system. When the compression was removed the blood flowed back to its previous level or to within 1 to 2 cm. of it. The level at which it became stationary represented the initial venous pressure by the "blood-down" method. Respiratory oscillations of the blood column, if present, and the close approximation between the "blood-up" and "blood-down" methods were usually indicative of a free system. A discrepancy of 1 to 2 cm. was regarded within the limits of error by this method and consequently ignored.<sup>4</sup>

- b) *The Moritz-Tabora method.* This method was employed in a small series of patients. The same "L" shaped manometer with a two way stop cock arrangement was filled with 5 per cent sodium citrate and fluid allowed to run into the punctured antecubital vein until it became stationary. The level of the fluid represented the initial venous pressure.

In many instances the systemic venous pressure was measured in the external jugular vein. When this was done an attempt was also made to level the neck so that the punctured cervical vein would approximate the theoretical horizontal plane of the caval openings in the right auricle. The skin overlying the vein was usually infiltrated with novocaine. To produce a "tourniquet" effect the subject was instructed to exhale forcibly with the glottis closed (Valsalva Maneuver).

<sup>4</sup> Whether the reading was obtained by the "blood-up" or "blood-down" methods, it will be subsequently referred to only as the initial venous pressure.



As soon as the cervical veins became noticeably fuller or tense the needle was inserted in the direction of the heart and the initial venous pressure was recorded in the same manner as for the antecubital vein. The respiratory oscillations were more marked when the external jugular vein was used.

## II. *The measurement of the effect of an increased venous return upon the initial venous pressure*

a) *Manual compression maneuver of the right upper abdomen.* While the needle was still in situ and the blood column was stationary at the level of the recorded initial venous pressure, the investigator placed the outstretched palm of his hand upon the subject's right upper abdominal quadrant and applied gradually increasing pressure for approximately one minute's duration. During this procedure the subject was instructed to breathe normally with his mouth open and his state of relaxation was checked by the passive elbow flexion maneuver. To enable the investigator to make such observations accurately the manometer was at times supported vertically by an assistant. The rise or fall of the blood column above or below the initial venous pressure level at the end of one minute's compression was recorded.

b) *Manual compression maneuver of the left lower abdomen.* The same procedure was followed as for (a), except that the left lower abdominal quadrant was compressed for one minute.

c) *Passive perpendicular elevation maneuver of the lower extremities.* The subjects were carefully trained to relax when the lower extremities were passively elevated to a position almost perpendicular to the trunk. After this preliminary coaching the initial venous pressure was measured either immediately or after the effects of abdominal compression were first determined.

## CIRCULATION TIMES

Circulation times with ether and saccharin or decholin were performed in the great majority of these patients. For details of the method the reader is referred to the original papers. The "arm to lung" and "arm to tongue" measurements served to define more fully the various circulatory syndromes—thereby making possible more accurate interpretations of characteristic venous pressure curves in these conditions.

## VENOUS PRESSURE CURVES IN NORMAL INDIVIDUALS

*The Normal Initial Venous Pressure.* Antecubital venous pressures were obtained in 670 "normal" men and women. In 624 or 93.2 per cent of this group the initial venous pressure ranged between 4 and 8 cm., in 29 individuals, or 4.3 per cent the initial venous pressure ranged between 2 and 4 cm., whereas in 17, or 2.5 per cent, the height of the initial venous pressure fell between 8 and 10 cm. The normality of these subjects was determined by the history, physical findings and blood flow studies. The "arm to tongue" circulation time by the saccharin or decholin methods was normal (9 to 16 sec.) in every case, and the "arm to

lung" circulation time with ether performed in 425 individuals, was also within the normal range (4 to 8 sec.).

*The Effect of Right Upper Abdominal Compression upon the Height of the Initial Venous Pressure Level.* In the entire series of 670 normal subjects whose initial venous pressure was determined, the level of the venous column was also recorded during one minute of sustained and gradually increasing compression of the right upper abdomen. In 89, or 13.3 per cent, the height of the blood column remained stationary, whereas in 581, or 86.7 per cent, the height of the venous column gradually fell a distance of from 0.5 to 2.5 cm. below the original level. As can be seen from Table I, a drop in venous pressure during right upper

TABLE I

*Antecubital initial venous pressure in "normal" individuals and the effect of right upper abdominal compression (venous pressure curve)*

| NUMBER OF INDIVIDUALS | INITIAL VENOUS PRESSURE<br><br><i>cm. of blood</i> | EFFECT OF ONE MINUTE OF SUSTAINED RIGHT UPPER<br>ABDOMINAL COMPRESSION ON HEIGHT OF INITIAL<br>VENOUS PRESSURE |                        |
|-----------------------|--|--|------------------------|
|                       |  | No. of individuals showing   |                        |
|                       |  | No rise or no fall   | Fall of 0.5 to 2.5 cm. |
|                       |  | <i>cm. of blood</i>  | <i>cm. of blood</i>    |
| 29*                   | 2-4  | 12   | 17                     |
| 116                   | 4-5  | 20   | 96                     |
| 168                   | 5-6  | 25   | 143                    |
| 210                   | 6-7  | 18   | 192                    |
| 130                   | 7-8  | 10   | 120                    |
| 17†                   | 8-10   | 4  | 13                     |
| Total: 670            |  | 89   | 581                    |

\* No evidence of peripheral failure (as evidenced by the history, physical findings and a normal arterial pressure).

† No evidence of heart failure (as determined by the history, physical findings and normal circulation time studies).

abdominal compression was encountered more frequently in those groups whose venous pressures were at a higher initial level. The greatest depression of the venous column during the upper abdominal compression maneuver was also observed in the group whose initial venous pressure was at the upper limit of normal although this relation did not obtain in all instances. In a group of 88 "normals" not included in the series (Table I) in whom venous pressure curves were obtained by puncturing an external jugular vein, right upper abdominal compression of one minute's duration caused a universal fall, the drop ranging between 1.5 and 3.5 cm. The values of the initial venous pressure in this group ranged between 3 and 8 cm.

Several factors which might influence the effect of right upper abdominal compression on the height of the venous pressure level were studied:

*Breathing.* As is already well known, hyperventilation of the lungs causes lowering of the normal initial venous pressure, an observation previously de-

scribed by Eyster, Fishberg and others. This was also true in a series of six carefully studied subjects. After the normal venous pressure curve was established in each instance, the subject was told to breathe rapidly and deeply. Fluctuations in venous pressure during an interval of about one minute were recorded. The antecubital venous tension fell progressively to a lower level and the drop in venous pressure during right upper abdominal compression was also less marked than during normal breathing (Table II). Although the fall on right upper abdominal compression during hyperventilation was less marked

TABLE II

*Effect of hyper-ventilation on venous pressure curves*

| CASE NO. | INITIAL VENOUS PRESSURE | EFFECT OF RIGHT UPPER ABDOMINAL COMPRESSION | VENOUS PRESSURE DURING RAPID AND DEEP BREATHING | EFFECT OF RIGHT UPPER ABDOMINAL COMPRESSION |
|----------|-------------------------|---|---|---|
|          | <i>cm. of blood</i>     | <i>fall or rise<br/>cm. of blood</i>        | <i>cm. of blood</i>                             | <i>fall or rise<br/>cm. of blood</i>        |
| 1        | 6                       | -1.5  | 3   | -.5   |
| 2        | 8                       | -2.5  | 4   | -1.5  |
| 3        | 7                       | -1  | 2.5   | -1  |
| 4        | 6                       | -2  | 3   | -.5   |
| 5        | 6.5                     | -2.5  | 2   | -.75  |
| 6        | 5                       | -1.5  | 3   |   |

TABLE III

*Effect of hypo-ventilation on venous pressure curve*

| CASE NO. | INITIAL VENOUS PRESSURE | EFFECT OF RIGHT UPPER QUADRANT COMPRESSION | INITIAL VENOUS PRESSURE DURING HYPO-VENTILATION | EFFECT OF RIGHT UPPER ABDOMINAL COMPRESSION |
|----------|-------------------------|--|---|---|
|          | <i>cm. of blood</i>     | <i>fall or rise<br/>cm. of blood</i>       | <i>cm. of blood</i>                             | <i>fall or rise<br/>cm. of blood</i>        |
| 7        | 6.5                     | -2   | 7.5   | -1  |
| 8        | 8                       | -2   | 8.5   | -1  |
| 9        | 5                       | -1   | 7.5   | 0   |
| 10       | 7                       | -2.5                                       | 9   | +1  |
| 11       | 6                       | 0  | 8   | +2  |

than during normal breathing, the downward trend during the compression maneuver was directly proportional to the height of the initial venous pressure.

Similar observations during hypo-ventilation (Table III) were also attempted in five patients but these were carried out with difficulty. After obtaining the venous pressure by the usual technique the patient was told to hold his breath or to breathe less often without discomfort and without straining. In general the venous pressure during this period of diminished breathing rose to a slightly higher level but the right upper abdominal compression effect on the venous pressure was less conclusive. Not only was the drop less marked in three subjects but in two of the subjects upper abdominal compression actually caused a rise in the level of the blood column. It was difficult to ascertain whether this

effect was due only to the partial elimination of the "sucking in" mechanism during inspiration or whether the rise represented a partial Valsalva effect. At any rate it emphasizes the importance of normal or deep breathing during manometric registration of the venous pressure when the abdomen is compressed.

LEVEL OF THE ARM IN RESPECT TO THE ASSUMED LEVEL OF THE HEART  
(TO DETERMINE EFFECT OF THE STATE OF INITIAL DISTENTION OR COLLAPSE OF THE VEINS ON THE HEIGHT OF THE VENOUS PRESSURE)

In accordance with hydrostatic principles, elevating or lowering the arm below the level of the heart causes an inverse effect upon the height of the antecubital venous pressure. In chests of large antero-posterior diameters, as in cases of emphysema, one cannot be certain whether the theoretical level corresponds to

TABLE IV  
*Effect of position of arm on venous pressure curve*  
(Below assumed level of heart)

| CASE NO. | INITIAL VENOUS PRESSURE WITH ANTECUBITAL SURFACE 5 CM. BELOW STERNUM (ASSUMED LEVEL OF HEART) | EFFECT OF RIGHT UPPER ABDOMINAL COMPRESSION | INITIAL VENOUS PRESSURE AFTER LOWERING ANTECUBITAL SURFACE TO LEVEL 10 CM. BELOW STERNUM (BELOW ASSUMED LEVEL OF HEART) | EFFECT OF RIGHT UPPER ABDOMINAL COMPRESSION |
|----------|---|---|---|---|
|          | <i>cm. of blood</i>   | <i>fall or rise cm. of blood</i>            | <i>cm. of blood</i>   | <i>fall or rise cm. of blood</i>            |
| 12       | 4   | 0   | 8   | -1  |
| 13       | 3   | 0   | 6.5   | -2  |
| 14       | 7   | -2  | 9.5   | -2  |
| 15       | 6   | -1  | 10  | -3  |
| 16       | 8   | -2.5  | 11  | -2.5  |
| 17       | 7   | -.5   | 11  | -1.5  |
| 18       | 6   | -1.5  | 9   | -2  |
| 19       | 5   | 0   | 7   | -.5   |
| 20       | 8   | -1  | 10  | -1  |
| 21       | 7   | 0   | 9.5   | 0   |
| 22       | 6.5   | -2  | 10  | -2.5  |

the actual level of the caval openings. Undoubtedly as Lyons (18) and his co-workers have shown, such topographical miscalculations must alter the height of the initial venous pressure. Although the level of the arm and the diameter of the chest are reflected in the height of the initial venous pressure, the abdominal compression effect persists with slight quantitative alterations only, regardless of the reference point at which the determination is made. To prove that the degree of initial distension (or collapse) of the veins does not significantly alter the abdominal compression effect, venous pressure curves were obtained by changing the reference point as follows:

1) After determining the initial venous pressure and the effect of right upper abdominal compression, the arm was lowered to a point about 10 cm. below the anterior border of the sternum, and the height of the venous pressure before and during right upper abdominal compression was recorded in eleven patients.

It is apparent from reviewing Table IV that when the veins, which may normally even be in a semicollapsed state, are partially distended by lowering the antecubital region below the assumed level of the right auricle, the depressing effect of right upper abdominal compression upon the height of the venous pressure not only persists, but, in the majority of cases, even becomes exaggerated. The latter fact is substantiated in seven of the eleven cases studied.

2) Similarly in eight patients the initial venous tension was intentionally lowered by elevating the antecubital surface to the level of the anterior border of the sternum (5 cm. above the theoretical or assumed level of the heart).

Although according to Table V right upper abdominal compression causes uniformly a lowering of the initial venous tension, the amplitude of the depression is less marked. This is undoubtedly due to the initial semi-collapsed state of the

TABLE V  
*Effect of position of arm on venous pressure curve*  
(Above assumed level of heart)

| CASE NO. | INITIAL VENOUS<br>PRESSURE WITH<br>ANTECUBITAL SURFACE<br>5 CM. BELOW STERNUM<br>(ASSUMED LEVEL OF<br>HEART) | EFFECT OF RIGHT<br>UPPER ABDOMINAL<br>COMPRESSION | VENOUS PRESSURE<br>AFTER ELEVATING<br>ANTECUBITAL SURFACE<br>TO LEVEL OF STERNUM<br>(ABOVE ASSUMED<br>LEVEL OF HEART) | EFFECT OF RIGHT<br>UPPER ABDOMINAL<br>COMPRESSION |
|----------|--|---|---|---|
|          | <i>cm. of blood</i>  | <i>fall or rise<br/>cm. of blood</i>              | <i>cm. of blood</i>   | <i>fall or rise<br/>cm. of blood</i>              |
| 23       | 4  | 0   | 2   | 0   |
| 24       | 6  | -2  | 2   | -.5   |
| 25       | 5  | -2.5  | 2   | -.5   |
| 26       | 7  | -2  | 4   | -1  |
| 27       | 8  | -2  | 3.5   | -.5   |
| 28       | 4.5  | -.5   | 1.5   | 0   |
| 29       | 7  | -1.5  | 4   | -1  |
| 30       | 4  | -1.5  | 2   | -.5   |

veins, which mechanically minimizes the depressing effect of right upper abdominal compression. However, it is the downward trend of the venous pressure during this procedure rather than the extent of the quantitative change that is significant.

#### RELAXED STATE OF INDIVIDUALS STUDIED (DURING ANAESTHESIA)

Venous pressure curves were obtained in 9 normal individuals during avertin anaesthesia (Table VI) and in 4 individuals during spinal anaesthesia (Table VII), administered prior to operation. The initial venous pressure in the avertinized patients ranged from 2.0 to 4.5 cm. On right upper abdominal compression the venous column in the manometer dropped in all instances, the drop ranging between 1.0 to 2.5 cm. Venous pressure measurements during spinal anaesthesia were made in a small group but the results show even more strikingly parallel trends. The venous pressure which was initially low showed a marked disproportionate drop (to zero levels in 2 instances) when the right upper abdomen was compressed. No measurements of the effect of left lower abdominal



compression were made during spinal anaesthesia. Circulation time with ether and saccharin was performed and found to be normal despite the depressed systemic venous pressure.

TABLE VI

*Venous pressure curves in anesthetized normal individuals (avertin anesthesia)*

| CASE NO. | INITIAL VENOUS PRESSURE | EFFECT OF RIGHT UPPER ABDOMINAL COMPRESSION | EFFECT OF LEFT LOWER ABDOMINAL COMPRESSION | EFFECT OF PASSIVE PERPENDICULAR ELEVATION OF LOWER EXTREMITIES |
|----------|-------------------------|---|--|--|
|          | <i>cm. of blood</i>     | <i>fall or rise cm. of blood</i>            | <i>fall or rise cm. of blood</i>           | <i>fall or rise cm. of blood</i>                               |
| 31       | 2                       | -1.5  | 0  | 0  |
| 32       | 4                       | -2.5  | -.5  | 0  |
| 33       | 3                       | -2  | 0  | 0  |
| 34       | 2                       | -1  | -.5  | 0  |
| 35       | 4.5                     | -2.5  | 2.0  | 0  |
| 36       | 4                       | -2.5  | -1.5                                       | 0  |
| 37       | 3                       | -1  | 0  | 0  |
| 38       | 2.5                     | -1  | 0  | 0  |
| 39       | 3                       | -2  | -1   | 0  |

TABLE VII

*Venous pressure curves in anesthetized normal individuals (spinal anesthesia)*

| CASE NO. | INITIAL VENOUS PRESSURE | EFFECT OF RIGHT UPPER ABDOMINAL COMPRESSION | CIRCULATION TIMES   |                           |
|----------|-------------------------|---|---------------------|---------------------------|
|          |                         |   | Ether "arm to lung" | Saccharin "arm to tongue" |
|          | <i>cm. of blood</i>     | <i>fall or rise cm. of blood</i>            | <i>time sec.</i>    | <i>time sec.</i>          |
| 40       | 2                       | -2  | 4½                  | 15                        |
| 41       | 1.5                     | -1  | 6                   | 13                        |
| 42       | 1.5                     | -1  | 5                   | 14                        |
| 43       | 2.5                     | -2  | 3.5                 | 15                        |

#### THE EFFECT OF LEFT LOWER ABDOMINAL COMPRESSION UPON THE HEIGHT OF THE INITIAL VENOUS PRESSURE LEVEL

The effect of left lower abdominal compression upon the height of the initial venous pressure was observed in about 242 patients (Table VIII). This procedure was usually executed as a sequel to the right upper abdominal maneuver, in order to establish conclusively that a positive hepato-jugular reflux phenomenon in right heart failure was not just a "diaphragmatic" or "liver" effect but one entirely dependent upon the following mechanisms: 1) impaired right ventricular function and 2) an increased venous return consequent to a heightened intra-abdominal pressure and 3) an increased circulating blood volume (inconstant factor). In the vast majority of instances in this series of 242 individuals, the left lower quadrant maneuver failed to change significantly the level of the blood column in the manometer, regardless of the abdominal pressure exerted, provided

that the individuals remained relaxed and continued to breathe normally. In only sixty-four individuals was left lower quadrant compression attended by a fall of the initial venous pressure level, which ranged between 0.5 and 2 cm. In five out of the nine avertin anaesthetized patients, however, pressure exerted upon the left lower quadrant of the abdomen caused a drop from about 0.5 to 2.0 cm. (Table VI).

A comparison of the effect during left lower quadrant compression with that obtained during right upper abdominal compression reveals a more consistent depressing effect on the height of the initial venous pressure during the latter maneuver.

TABLE VIII

*Antecubital initial venous pressure in "normal" individuals and the effect of left lower abdominal compression (venous pressure curve)*

| NUMBER OF INDIVIDUALS | INITIAL VENOUS PRESSURE | EFFECT OF ONE MINUTE OF SUSTAINED LEFT LOWER ABDOMINAL COMPRESSION ON HEIGHT OF INITIAL VENOUS PRESSURE LEVEL |                        |
|-----------------------|-------------------------|---|------------------------|
|                       |                         | No rise or fall   | Fall of 0.5 to 2.0 cm. |
|                       | cm. of blood            | cm. of blood  | cm. of blood           |
| 6                     | 2-4                     | 5   | 1                      |
| 45                    | 4-5                     | 33  | 12                     |
| 68                    | 5-6                     | 53  | 15                     |
| 77                    | 6-7                     | 57  | 20                     |
| 42                    | 7-8                     | 28  | 14                     |
| 4                     | 8-10                    | 2   | 2                      |
| Total.....            |                         | 178   | 64                     |

#### THE EFFECT OF PASSIVE PERPENDICULAR ELEVATION OF LOWER EXTREMITIES UPON THE HEIGHT OF THE INITIAL VENOUS PRESSURE LEVEL

After measuring the initial venous pressure in 64 normal individuals, the venous return to the heart was increased by elevating the lower extremities in a passive manner to a position where they were almost perpendicular to the trunk. The effect of this procedure upon the height of the antecubital pressure was recorded.

As can be seen from the accompanying table (Table IX) passive perpendicular elevation of the lower extremities caused either no noticeable effect or a rise which in some instances reached as high as 5 cm. above the initial level.

Although the individuals under investigation received careful preliminary coaching to encourage complete relaxation during passive elevation of their lower extremities, it is doubtful if this state was achieved in 43 of the subjects in whom the maneuver caused a rise of the antecubital venous pressure. This statement is based on observations obtained during anaesthesia in nine "completely relaxed" individuals (Table VI) in whom passive elevation of the left lower extremity failed to affect the level of the venous column in the manometer. This suggests that the rise obtained in normal unanaesthetized individuals during

this maneuver may represent not only incomplete relaxation, but actually active, clinically undetectable muscular contraction. Because the abdominal compression maneuver in anaesthetized and unanaesthetized individuals does show comparable or parallel trends which are in marked contrast to the inconstant results obtained with the lower extremity maneuver, the latter procedure was regarded as an unreliable method of studying the effect of an increased venous return on the functional status of the right ventricle.

TABLE IX

*Antecubital initial venous pressure in "normal" individuals and the effect of passive perpendicular elevation of lower extremities*

| NUMBER OF INDIVIDUALS | INITIAL VENOUS PRESSURE | EFFECT OF PASSIVE PERPENDICULAR ELEVATION OF LOWER EXTREMITIES OF ONE MINUTES DURATION ON HEIGHT OF INITIAL VENOUS PRESSURE LEVEL |                         |
|-----------------------|-------------------------|---|-------------------------|
|                       |                         | No rise or fall   | Rise of 0.5. to 5.0 cm. |
|                       | <i>cm. of blood</i>     | <i>cm. of blood</i>   | <i>cm. of blood</i>     |
| 3                     | 2-4                     | 2   | 1                       |
| 14                    | 4-5                     | 6   | 8                       |
| 20                    | 5-6                     | 7   | 13                      |
| 19                    | 6-7                     | 4   | 15                      |
| 8                     | 7-8                     | 2   | 6                       |
| Total.....            |                         | 21  | 43                      |

## DISCUSSION

The venous pressure curve is best recorded by measuring the level of the initial venous pressure and then registering the height (rise or fall) of the blood column during right upper abdominal compression. Although left lower abdominal compression may give comparable results, the right upper abdominal maneuver seems more satisfactory for routine use because in "normals" this method of increasing the intra-abdominal tension also elicits in a high percentage of cases a characteristic circulatory phenomenon, namely a fall in the venous pressure level (negative hepato-jugular reflux phenomenon), which serves as a valuable corroborative sign of normal right ventricular function. By this means, characteristic venous pressure curves are obtained. The accompanying charts represent such curves encountered in normal subjects.

Determination of the venous pressure curve serves to minimize the role of extra-cardiac factors which occasionally operate to falsely effect an elevated initial venous pressure where none actually exists. Whether these extra-cardiac factors represent variations in intrathoracic pressure, errors in technique, or a false leveling of the zero point (as described by Lyons), the frequency of error suggests that the methods in current use are not entirely adequate. With the method presented in this paper, the functional status of the right heart can not only be suspected from the oft unreliable initial venous pressure reading, but can actually be confirmed at the same time by observing the rise or fall of the venous pressure

level during sustained upper abdominal compression. Without exception, an immobile or depressed blood column during this maneuver provides a pathognomonic sign of a normally functioning right ventricle at rest, regardless of the numerical value of the initial systemic venous pressure. In other words, even an elevated initial venous pressure does not imply the presence of a functionally handicapped right ventricle if right upper abdominal compression causes an actual depression of the initial venous pressure level in the manometer. Initial elevation of the venous pressure, if not due to heart disease, may also result from local circulatory disturbances consequent to partial interference with the venous return from the brachio-cephalic portion of the body. Such elevated initial venous pressure readings with a drop on right upper abdominal compression may also be observed for example in unilateral tension pneumothorax, and in partial superior vena cava occlusion. In these situations, the upper abdominal maneuver is invaluable because it testifies unequivocally to the presence of normal right ventricular efficiency despite the elevated initial reading.

Regardless of the reference point employed, the trend of the venous pressure curve remains essentially unchanged provided that the subject breathes normally and remains relaxed during the procedure. With the reference point 5 cm. below the anterior border of the sternum the initial venous pressure usually ranges between 4 and 8 cm. with occasional readings as low as 2 cm. and as high as 10 cm. On right upper abdominal compression however, the venous pressure remains either unchanged or is lowered from 0.5 to 2.5 cm. The variations in the right upper quadrant effect are dependent upon the state of the initial fullness of the veins as shown in Tables IV and V. The reference point as proposed by Lyons (100 cm. anterior to the skin of the back) eliminates the factor of chest diameter but it yields venous pressure readings for "normals" which are higher. Even so, the right upper quadrant compression effect persists and it may even be exaggerated because the veins are initially fuller. It is well to emphasize again that isolated venous pressure measurements serve only as a rough measure of the functional capacity of the right heart. With upper abdominal compression, measurements of the venous pressure present trends which give it greater accuracy even if taken from an indiscriminate reference point. It is reasonably safe to conclude that the effect of the abdominal maneuver upon the height of the venous pressure serves as a most reliable index of right ventricular function at rest.

Although this fall of the venous pressure during right upper abdominal compression occurs only in 81 per cent of the normal subjects tested this phenomenon is probably universally true if carried out under completely relaxed conditions. The results in Tables VI and VII which reveal measurements obtained during general and spinal anaesthesia support this view. As has been previously mentioned, a fall in venous pressure can always be demonstrated when the external jugular vein is the site chosen for the measurement.

The mechanism of the gradual drop in venous pressure during abdominal compression in normal individuals is readily explained despite the occurrence of an increased venous return which follows the rise of intra-abdominal tension. The

normal heart accommodates itself promptly to the increased work by an increased output in accordance with Starling's law, and thereby maintains a normal venous pressure in the systemic veins. However, when the squeezing out effect of the splanchnic blood depots is complete, the venous return from the lower half of the body diminishes or becomes even momentarily completely halted. This occurs because abdominal compression, after the initial venous forward thrust, exerts a "tourniquet effect" upon the distal inferior vena cava probably somewhere in the subhepatic region which results in stasis within the tributaries of that vessel. The resulting diminished venous return engenders a diminished cardiac output which lasts until the arbitrary period of compression (one minute) is at an end. As a result of the diminished output, the systemic venous pressure falls to a point which is never more than 2.5 cm. below the original or initial level. A prompt drop in the venous pressure level during upper abdominal compression, observed in several cases of anemia (decreased blood viscosity and consequently a more sensitive manometric system), suggests another possible explanation. When the stream of ascending blood in the inferior vena cava and portal systems is gradually lessened or abolished by upper abdominal compression, there develops a diminished resistance to the current returning blood from the tributaries of the superior vena cava. As a consequence, there is greater emptying of the veins from the upper portion of the body which is promptly reflected in a drop of the venous pressure in the antecubital and external jugular veins. As one would expect, the venous pressures in the tributaries of the inferior vena cava becomes elevated because the blood pools in the lower half of the body when the abdomen is compressed. Measurements of the femoral venous pressure in twenty-eight individuals during this maneuver have confirmed this view. The venous pressures rose from a normal level of 4 to 8 cm. to levels which ranged between 20 to 35 cm., the rise being proportional to the degree of abdominal compression employed.

#### CONCLUSIONS

1) The application of the Pasteur-Rondot (hepato-jugular reflux) phenomenon to manometric measurements of the venous pressure yields characteristic venous pressure curves for normal and abnormal circulatory states.

2) Venous pressure curves are of definite aid in the diagnosis of borderline and frank cases of right heart failure.

3) The venous pressure curve, in subjects whose right ventricular function *at rest* is intact, is characterized by an initial venous pressure ranging between 4 and 8 cm. and a gradual drop of the venous pressure level (0.5 to 2.5 cm.) during sustained right upper abdominal compression for one minute.

4) Although extra-cardiac factors such as the selected zero point, arm abduction, etcetera, may also exert some influence on the character of the venous pressure curve—they are relatively less significant with this technique since their influence will be manifest predominantly, if not entirely, in the initial venous pressure reading (first half of curve) and not in that portion which deals with the effect of right upper abdominal compression upon the height (rise or fall) of the



venous column in the manometer (second half of curve). Thus, even an initial venous pressure reading of 10 to 12 cm. if attended by a fall of from 0.5 to 2.5 cm. (or even a fall of 3.5 cm. if the external jugular vein is employed) is indicative of normal right ventricular function.

5) The fall of the venous pressure level during right upper abdominal compression in normal subjects can be regarded as a *negative hepato-jugular reflux phenomenon*—which probably owes its origin to several factors:

a) The "tourniquet" effect of the abdominal maneuver which, following the initial increased venous return, compresses the inferior vena cava and causes pooling of blood in the lower half of the body during the latter half of the one minute period of abdominal compression.

b) A lessened cardiac output following the initial "squeezing" out effect of the splanchnic viscera and

c) a lessened resistance to the blood flowing into the right auricle from the superior vena cava following the increased initial return through the inferior vena cava.

6) In incipient and frank right heart failure, right upper abdominal compression causes a rise of the venous pressure which is proportional to the severity of the right ventricular weakness and to other factors e.g. circulating blood volume, and total venous capacity. This *positive hepato-jugular reflux phenomenon* and the factors which operate in its genesis will be presented in a subsequent publication.

The author wishes to express his thanks to Dr. Arthur M. Fishberg, whose guidance and inspiration helped immeasurably in the satisfactory completion of this phase of the problem in circulatory dynamics.

#### BIBLIOGRAPHY

- 1) LEWIS, SIR THOMAS: Diseases of the Heart. New York, The MacMillan Co., 1933.
- 2) HALES, STEPHEN: Statical Essays, London, 1769.
- 3) STARLING, ERNEST HENRY: The Linaere Lecture on The Law of The Heart, London, 1918.
- 4) HENDERSON, YANDELL: Tonus and the Venopressor Mechanism. The Clinical Physiology of a Major Mode of Death. Medicine 22: 223, 1943.
- 5) EYSTER, JOHN AUGUSTUS ENGLISH: Clinical Aspects of Venous Pressure, New York, 1929.
- 6) VILLARET, MAURICE, SAINT-GIRONS, FRANCOIS AND JUSTIN-BESANCON, L.: La pression veineuse peripherique, Paris, 1930.
- 7) POGANY: Deutsch. Arch. f. Klin. Med., 171: 185, 1931.
- 8) FISHBERG, A. M.: Heart Failure, Philadelphia, Lea & Febiger, 1937.
- 9) PASTEUR, W. A.: Note on a New Physical Sign of Tricuspid Regurgitation, Lancet, 2: 524, 1885.
- 10) RONDOT, E.: Le Reflux Hepato-Jugulaire. Hazet. Hebd. d. Sc. Med. de Bordeaux, 19: 569, 1898.
- 11) PLESCH, J.: In Kraus und Brugsch, Spezielle Pathologie und Therapie Innere Krankheiten pt. 2, 4: 1260, 1925.
- 12) OPPENHEIMER, B. S. AND HITZIG, W. M.: The Use of Circulatory Measurements in Evaluating Pulmonary and Cardiac Factors in Chronic Lung Disorders, Trans. A. Am. Physicians, 2: 108, 1936.

- 13) HITZIG, W. M.: Measurement of the circulation time from the antecubital veins to the Pulmonary Capillaries. *Proc. Soc. Exper. Biol. & Med.*, 31: 995, 1934.  
The use of ether in measuring the circulation time from the antecubital Veins to the pulmonary capillaries. *Am. Heart J.*, 10: 1080, 1935.
- 14) FISHBERG, A. M., HITZIG, W. M. AND KING, F. H.: Measurement of Circulation Time with Saccharin. *Proc. Soc. Exper. Biol. & Med.* 30: 651, 1933.
- 15) DEUTSCH, J. WINTERNITZ, M. AND BRUELL, Z.: Eine Klinische brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholininjertion, *Med. Klin.*, 27: 986, 1931; *ibid.* 28: 831, 1932.
- 16) TAYLOR, F. A., THOMAS, A. B., AND SCHLECTER, H. G.: Direct Method for Estimation of Venous Pressure, *Proc. Soc. Exper. Biol. & Med.*, 27: 867, 1930.
- 17) MORITZ, F., AND VON TABORA, D.: Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exact zu bestimmen, *Deutsch. Arch. f. Klin. Med.*, 98: 475, 1910.
- 18) LYONS, R. H., KENNEDY, J. A. AND BURWELL, C. S.: The Measurement of Venous Pressure by The Direct Method. *Am. Heart. J.*, 16: 675, 1938.
- 19) OPPENHEIMER, B. S., HITZIG, W. M. AND NEUHOF, H.: Chronic Constrictive Pericarditis; Medical and Surgical Aspects. *J. Mt. Sinai Hosp.* 7: 270, 1941.
- 20) HITZIG, W. M.: Constrictive Pericarditis, an Atypical Case. Extreme Ascites, Cure by Pericardiectomy. *J. Mt. Sinai Hosp.* 10: 722, 1944.
- 21) HITZIG, W. M.: On Mechanisms of Inspiratory Filling of the Cervical Veins and Pulsus Paradoxus in Venous Hypertension. *J. Mt. Sinai Hosp.* 8: 625, 1942.

## NORMAL VENOUS PRESSURE CURVE IN A LARGE ANTECUBITAL VEIN

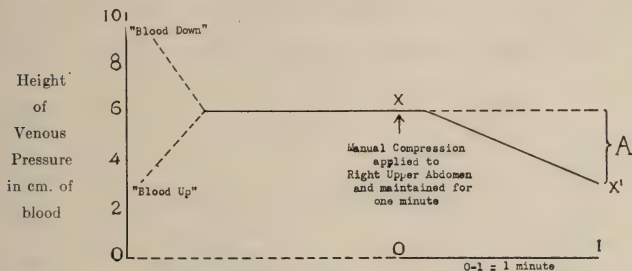


FIG. 1

With the cardiac reference point employed in this investigation the normal initial venous pressure (initial phase of venous pressure curve) ranges between 4 and 8 cm. although values as low as 2 cm. and as high as 10 cm. have not infrequently been observed. The fall of the initial antecubital venous pressure level during manual compression of the right upper abdomen (phase of abdominal compression) ranges between 0 and 2.5 cm. (A). The maximum fall (X to X') in normal subjects during one minute of upper abdominal compression usually does not exceed 2.5 cm.

The fall of the venous pressure level during the phase of abdominal compression (negative hepato-jugular reflex phenomenon in contrast to the positive hepato-jugular reflex phenomenon as observed in right heart failure) may be regarded as a pathognomonic sign of a normally functioning right ventricle at rest. Variation in the position of the reference point yields corresponding quantitative variations in the fall of the venous pressure level during manual compression of the abdomen, the degree of fall bearing a direct relationship to the height of the initial venous pressure (as seen in the initial phase of the venous pressure curve).

The fall of the venous pressure level during the phase of abdominal compression in normal subjects probably has the following genesis. The normal right heart accommodates itself promptly to the increased venous return engendered during the initial period of abdominal compression. Because of stasis of a major portion of the circulating blood volume in the lower half of the body due to inferior vena cava compression produced by manual compression of the right upper abdomen, the decreased venous return that ensues during the final period of abdominal compression, allows greater emptying of blood returning from the upper half of the body through the superior vena cava, which is reflected in the venous pressure by a gradual fall in the venous pressure level during the one minute phase of abdominal compression.

# NORMAL VENOUS PRESSURE CURVE IN A LARGE EXTERNAL JUGULAR VEIN

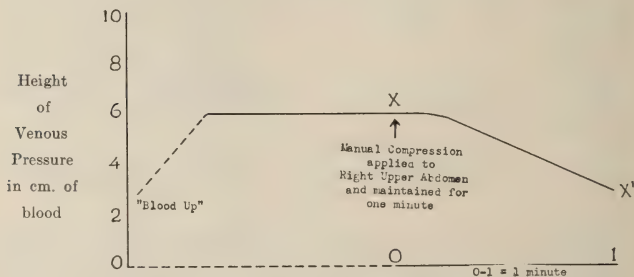


FIG. 2

A more accurate evaluation of right heart function is obtained when the venous pressure curve is measured in an external jugular vein. The greater accuracy of this measurement is evidenced by the universal fall of the venous pressure level during the phase of abdominal compression, which may in some instances show a maximum depression (X to X') of the venous pressure level of 3 to 3.5 cm. The greater sensitivity of the manometric system when the external jugular vein is employed is largely due to greater size of the vein and its proximity to the heart. The initial venous pressure in the external jugular vein ranges between 3 and 8 cm. in normal subjects.

NORMAL VENOUS PRESSURE CURVES IN A CASE OF CIRRHOSIS (LAËNNEC)  
WITH MASSIVE ASCITES AND NORMAL CARDIAC FUNCTION

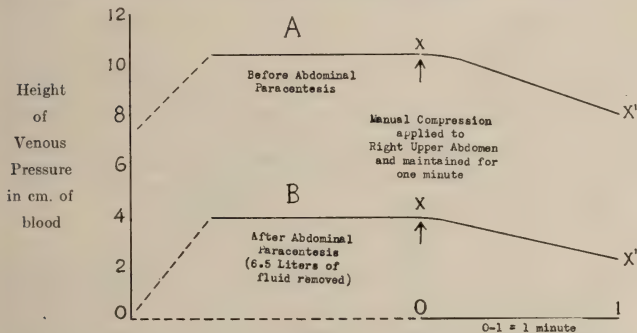


FIG. 3

These curves demonstrate the effect of ascites and its removal on the venous pressure curve in a subject whose normal cardiac function was established clinically and confirmed objectively by normal circulation times with ether and saccharin.

Although in A the initial venous pressure is higher and the fall of the venous pressure level during right upper abdominal compression (X to X') is more marked, both venous pressure curves A and B bear a distinctly normal pattern. The heightened initial venous pressure in A must be attributed to displacement by the ascitic fluid of blood from the compressed splanchnic or intra-abdominal depots to the peripheral systemic veins.

These observations also suggest that a drop of the venous pressure level during upper abdominal compression expresses more accurately the functional efficiency of the right ventricle at rest than does an isolated initial venous pressure reading whose magnitude and accuracy are not infrequently determined by a number of extracardiac factors, one of which is the location of the reference (or zero) point.



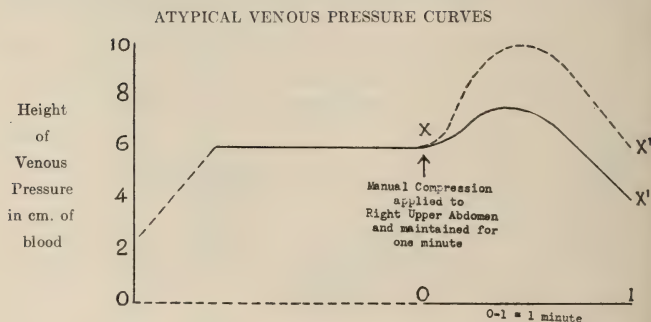


FIG. 4

Atypical venous pressure curves are observed at times not only in normal subjects but also in borderline or incipient right ventricular dysfunction. It consists of a normal initial venous pressure and a slight (not more than 2 to 4 cm.) but prompt rise of venous pressure level during manual right upper abdominal compression with a progressive fall to a previous or even lower level despite the maintenance of compression for one minute.

This type of venous pressure curve may be obtained under a variety of conditions which are:

1) Faulty technique in normal subjects due to incomplete relaxation or subject holding his breath (partial Valsalva maneuver).

2) Polycythemia Vera in which the increased circulating blood volume leads, as a result of abdominal compression, to an increased venous return which temporarily "overwhelms" the right auricle and is promptly reflected in a transient heightening of the venous pressure level. The normal right ventricular functional capacity eventually depresses this initial rise to its previous or to even a lower level.

3) Left ventricular failure associated with right ventricular strain and possible incipient right ventricular failure (?).

4) "Compensated" cor pulmonale whose incipient right ventricular weakness or failure may be first revealed by this type of curve.

CONTRASTING CHARACTERISTIC VENOUS PRESSURE CURVES OBSERVED IN NORMAL AND ABNORMAL CIRCULATORY STATES

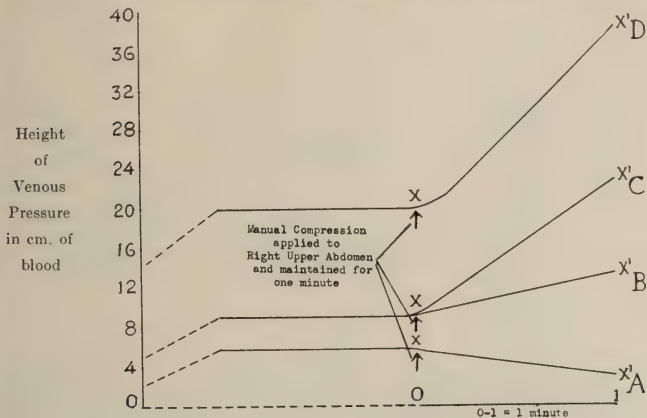


FIG. 5

A. *Normal Venous Pressure Curve.* Represents a normally functioning right ventricle at rest. This type of curve may also be obtained during the asymptomatic intervals of left sided heart failure (without coexistent right ventricular strain), and even during the active phase of bronchial asthma.

B. *Abnormal Venous Pressure Curve* which is characteristically obtained in either,

1) incipient right heart failure as in the initial stages of a decompensating chronic or acute cor pulmonale due to long standing broncho-pulmonary disease, lymphangitic carcinomatosis of the lungs or massive pulmonary embolization) and in early right ventricular strain secondary to failure of the left side of the heart due to rheumatic, luetic, arterio-sclerotic or hypertensive disease, and

2) in the compensating stages of moderate right heart failure and marked or frank right heart failure—the change in the character or magnitude of the curve representing a satisfactory therapeutic response to routine cardiac measures (digitalis, mercurial xanthine or ammonium chloride diuresis with salt and fluid restrictions, etc.), altho the improved curve never assumes a normal pattern.

C. *Abnormal Venous Pressure Curve* which represents a moderate degree of right heart failure and is due to either,

1) a more advanced stage of right heart weakness as expressed in figure 5B or

2) the compensating stage of frank right heart failure, the latter having responded to bed rest and the usual cardio-therapeutic measures.

D. *Abnormal Venous Pressure Curve* characteristically observed in frank right heart failure (see the causes mentioned under B). Extremely abnormal curves bearing this type of pattern, especially during the phase of manual compression of the right upper abdomen, have been observed in cases of hypodiastolic failure due to constrictive pericarditis.

ABNORMAL VENOUS PRESSURE CURVE IN A CASE OF ATYPICAL CONSTRUCTIVE PERICARDITIS. DEMONSTRATION OF THE EFFECT OF MASSIVE ASCITES AND ITS REMOVAL ON THE VENOUS PRESSURE CURVE

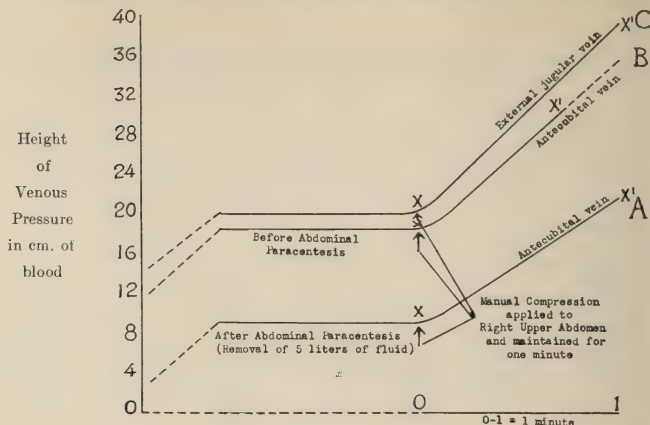


FIG. 6

This case, which was previously reported by Oppenheimer, Neuhoef and Hitzig (19) and again by Hitzig (20), emphasizes the value of the venous pressure curve in the diagnosis of this type of circulatory syndrome. In this case the ascites was attributed to cirrhosis of the liver for a period of nine years. One hundred fifty-two paracenteses were carried out and several major operations to encourage the absorption of abdominal fluid were performed—all without therapeutic effect. The diagnosis of hypodiastolic failure on the basis of constrictive pericarditis was made following the determination of the antecubital venous pressure curve which revealed an initial venous pressure of 18.5 cm. with a rise of 11.5 + cm. (over top of manometer) on right upper abdominal compression (B). The venous pressure curve in the external jugular vein yielded an initial venous pressure of 20 cm. and a rise of the venous pressure level to 39.25 cm. on right upper abdominal compression (C). This diagnosis was corroborated by the benign clinical course of long duration, the relative well-being of the patient and the absence of enlargement of the heart. Following the removal of 5 liters of ascitic fluid, doubt was cast on the above diagnosis because the venous pressure curve (A) showed a normal initial venous pressure of 9 cm. (8 cm. and 7 cm. on two subsequent days). It was argued, however, that the lowered initial venous pressure following emptying of the abdomen was not as significant in the evaluation of impaired right ventricular function as was the response of the initial venous pressure level to sustained right upper abdominal compression, which in this case showed a rise, which ranged from 9 to 12.5 cm. on different days. The venous pressure curve, as seen in B, despite the normal initial venous pressure reading was regarded as characteristic of moderately severe right heart failure (fig. 5C) and pericardiectomy for constrictive pericarditis was consequently urged. As the peritoneal fluid reaccumulated during the patient's further hospital stay, the initial venous pressure gradually rose again to a higher level (17 to 18 cm.). Again following abdominal paracentesis the initial venous pressure dropped to the previous normal level and right upper abdominal compression again yielded the previously recorded rise of 9.5 to 12 cm. A logical explanation for the elevated initial venous pressure was displacement of the intra-abdominal circulating blood volume to the peripheral veins, the cause of this displacement being ascites which by compressing the splanchnic blood depots reduced the "blood-holding" capacity of the intra-abdominal veins. This phenomenon was only partially observed in cirrhosis of the liver with massive ascites (fig. 3). The initial venous pressure in uncomplicated cirrhosis was elevated but to a much lesser degree and right upper abdominal compression yielded a falling venous pressure level, which is readily explained by the existence of normal right ventricular function and an essentially unchanged circulating blood volume.

To comprehend the character of the venous pressure curve after removal of ascitic fluid it was decided to mimic the effect of ascites by employing an inflated abdominal compression bag as used in Genito-urinary radiography. With the aid of this bag the abdomen was compressed and the height of the initial venous pressure and the super-added effect of right upper abdominal compression on the height of the initial venous pressure level were recorded as shown in Figure 7.

SCHEMATIC REPRESENTATION OF ABDOMINAL COMPRESSION BY ASCITES, BY HAND (MANUAL HEPATO-JUGULAR REFLEX PHENOMENON) AND BY INFLATED RUBBER BAG (TO MIMIC ASCITES) ON THE VENOUS PRESSURE CURVES IN A CASE OF ATYPICAL CONSTRUCTIVE PERICARDITIS

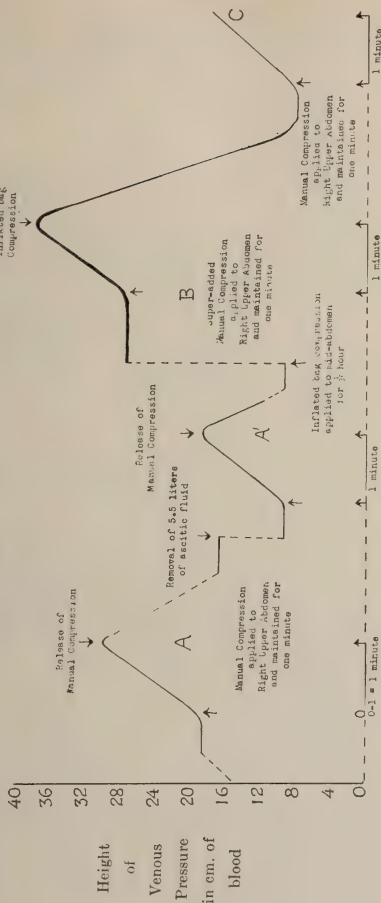


FIG. 7

The venous pressure curve prior to abdominal paracentesis was found to be abnormal (A) in both phases of the curve (the initial venous pressure phase and the phase of abdominal compression). After removal of the ascitic fluid, the venous pressure curve which revealed a normal initial venous pressure phase was again recorded (A'). The midabdomen was then compressed with the inflated compression bag without causing any discomfort to the patient. When circulatory equilibrium became established the venous pressure was again measured and found to be elevated to 27.5 cm. (It is of interest to mention that the venous pressure elevation with the inflated bag could be readily controlled by altering the degree of abdominal compression.) Additional manual compression with the palm of the outstretched hand was then applied and a superimposed rise of the venous pressure was then obtained (B). When the inflated bag pressure was completely released, the initial venous pressure returned to the previous normal level and a venous pressure curve similar to A' was obtained when the right upper abdomen was manually compressed (C).

At the operation constrictive pericarditis was found and a two stage pericardiectomy was eventually performed. The patient is still alive seven years after cardiac surgery.

In this case the persistence of an abnormal venous pressure curve of the type seen in moderately severe right heart failure was instrumental in the correct evaluation of the clinical picture, despite the fact that a normal initial venous pressure phase was obtained following removal of the ascites.

**ABNORMAL VENOUS PRESSURE CURVES IN SUPERIOR VENA CAVA OCCLUSION  
AND IN OCCLUSION OF ITS LARGE TRIBUTARIES (AXILLARY OR  
SUBCLAVIAN VEIN OCCLUSION)**

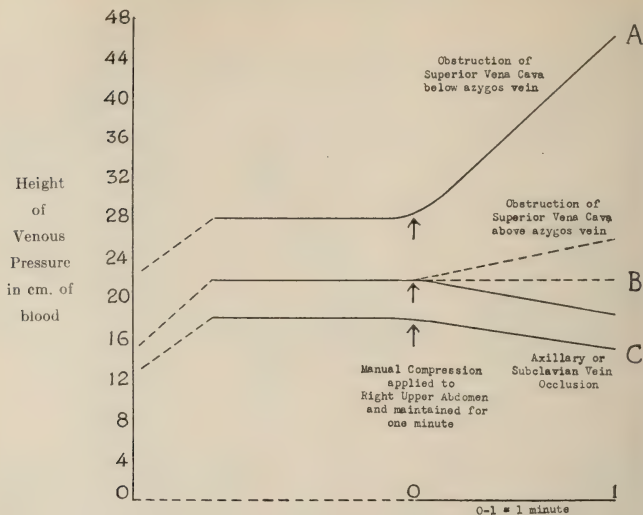


FIG. 8

The venous pressure curve in superior vena cava occlusion depends upon (1) the degree of the occlusion and (2) the site of the occlusion (whether it is above or below the azygos vein).

When the occlusion is *above the azygos vein* (B) the initial venous pressure will be high depending upon the degree of occlusion but during right upper abdominal compression, the venous pressure level will either fall, remain unchanged or show a slight rise from 2 to 4 cm. Except for a similarly elevated initial venous pressure this curve is in marked contrast to the venous pressure curve obtained in frank right heart failure (fig. 5D), and may be employed in the differential diagnosis of these two conditions.

When the occlusion is *below the azygos vein* (A), the venous pressure curve (except for the initial venous pressure which may be at a higher range) will mimic very closely the curve of frank right heart failure—although the pathologic physiology of the rise in the initial venous pressure during right upper abdominal compression is totally different and unrelated to the genesis of the “hepato-jugular reflex” phenomenon in frank right heart failure. In the latter, the venous return to the heart is generally increased by the abdominal maneuver, whereas in superior vena cava occlusion it may actually be decreased during the period of abdominal compression. In superior vena caval syndrome, the rise during right upper abdominal compression represents interference with the venous return from the superior vena cava which because of the occlusion below the azygos vein must empty itself entirely through its superficial and deep collaterals that drain into the inferior vena cava. This manual compression of the upper abdomen will, therefore, temporarily obstruct the venous flow from the upper part of the body and exert a “tourniquet” effect on the superior vena caval system, causing a diminished venous return to the heart and a rise in the venous pressure level during the duration of abdominal compression. Other circulatory criteria which distinguish obstruction below the azygos from obstruction above the azygos vein have been briefly mentioned by Hitzig (21) and will be published in greater detail in a paper on “The Circulatory Dynamics in Superior Vena Cava Occlusion.”

The venous pressure curve in subclavian and axillary vein occlusion (C) consists of a high initial venous pressure and a slight fall of the venous pressure level during right upper abdominal compression. This fall if present in the presence of a high initial venous pressure is significant—since its occurrence allows the conclusion that right ventricular function at rest is fully intact and that the high initial venous pressure is primarily of extra-cardiac or peripheral origin.



# ESSENTIAL HYPERTENSION ASSOCIATED WITH UNILATERAL DISEASE OF THE KIDNEYS

## A REPORT OF TWO CASES WITH APPARENT RELIEF FOLLOWING NEPHRECTOMY

A. HYMAN, M.D., AND H. E. LEITER, M.D.

In recent years, more careful attention and study of the kidneys have been carried out in patients with essential hypertension. For a time, there was a wave of enthusiasm towards nephrectomy in such individuals where unilateral surgical disease of the kidney was found. Case reports appeared in the literature where the previously elevated blood pressure returned to normal or dropped appreciably after removal of the diseased kidney. Some of these patients had been followed post-operatively for a number of years, while others were of such short follow-up that the late result was still in question.

The present concensus of opinion is that only a small percentage of those people with essential hypertension and unilateral disease of the kidneys may hope for a return of the tension to normal after nephrectomy. This point must be emphasized because it is obviously unjust to remove a good functioning kidney where conservative medical or surgical treatment may give the patient additional reserve of renal parenchyma. Where the urologist finds the indications for nephrectomy regardless of hypertension, this should be done. It is in the other group of patients that the decision of the type of surgery indicated is difficult. Here one must weigh the urologic as well as the hypertensive factors before deciding upon the preferable method of attack.

The main purpose of this paper is to present two unusual cases of essential hypertension associated with unilateral disease of the kidney. One case has been followed for a sufficient period of time to show the benefits of nephrectomy. Although the follow-up in the other case is shorter, the symptomatic and objective clinical improvement has been noteworthy.

### CASE REPORTS

*Case 1. History:* J. E., male, aged 39 years, was first seen at the office June 3, 1941 complaining of headaches.

His medical history dated back to September 1929 when he developed an attack of left renal colic with blood and pus in his urine. He was cystoscoped several times until he finally passed a ureteral calculus in January 1930. At that time he was told that the left kidney was damaged. Because the pyuria persisted, he consulted a urologist in Frankfort who told him that his systolic blood pressure was 155. Nothing significant occurred until 1936 when his wife died. This resulted in a "nervous breakdown" and the development of rheumatic pains and aches in various joints of the extremities. Although he was confined to bed at this time for about two months, his attending physician told him that his blood pressure was high and that his urine contained blood and pus.

The complaint of headaches began in 1939 about a year and one-half prior to admission to the hospital. These occurred in the region of the occipital area and extended down to the adjacent part of the neck. They occurred almost daily, lasted for many hours, and were relieved by acetyl salicylic acid. The headaches gradually became more severe, and three months ago he began to note precordial pain and pain in his cervico-dorsal spine.

There were no gastro-intestinal, cardiovascular or other neurologic symptoms. He voided every four hours during the day and twice at night.

*Examination:* Patient appeared well nourished. The head and neck were normal. The fundi revealed somewhat narrowed arteries with exaggerated light reflex. The lungs were clear. The heart was enlarged to the left but otherwise normal except for accentuation of the 2nd aortic sound. The abdomen, external genitalia and prostate were normal. The blood pressure was 182 systolic and 122 diastolic.

*Laboratory Data:* The urine showed a faint trace of albumin and a moderate number of single pus cells per low power field. Blood urea nitrogen, 16 mgm. per cent. Hemoglobin, 90 per cent. Red and white blood cell counts were normal.

*X-ray examination:* The right kidney outline was normal in size, shape and position. The left kidney outline was about one-half the size of the right kidney; it was situated high up, and within it two small calcific shadows were visible.

*Intravenous Urography:* The right renal pelvis, calices and ureter were normal. The left kidney was hypoplastic—or atrophic. Visualization was adequate and showed a small renal pelvis with minor caliceal changes such as usually seen in chronic pyelonephritis. Some of the minor calices extended close to the periphery of the kidney. The lower end of the left ureter was moderately dilated.

*Cystoscopy:* The bladder was mildly inflamed. The right ureter orifice was normal, and the left patulous. Indigo-carmin given intravenously appeared in strong concentration from the right kidney, and in somewhat weaker concentration from the left kidney. The urine from the right kidney failed to show pus, while that from the left kidney showed a small amount of pus.

*Course:* It was decided to observe this patient over a period of time. He was given one-half grain of phenobarbital four times daily for sedation. The following blood pressures were recorded in the ensuing weeks: 182/122; 210/140; 210/140; 200/130. Because of the severe, persistent headaches, the high diastolic blood pressure and the development of a few hemorrhages and exudates in his fundi, it was decided to admit him to the hospital for nephrectomy in the hope that improvement in his tension might follow. During his pre-operative stay in the hospital and under complete bed-rest with sedatives, his blood pressure was recorded as 200 systolic and 120 diastolic.

*Operation:* On October 7, 1941 (H. E. L.) a left lumbar nephrectomy was performed.

The kidney was exposed through a left lumbar incision; it was about one-half to one-third the normal size and it was situated very high and under the diaphragm. It was adherent to the left adrenal gland and was surrounded by a moderate degree of peri-nephritis.

*Pathology:* Chronic pyelonephritis with considerable arteriosclerosis.

*Post-operative Course:* Entirely uneventful. The wound healed by primary union, and the patient was discharged from the hospital on the sixteenth day. His headaches were entirely gone and he felt symptomatically improved. The recorded blood pressures during his hospital stay were as follows:

|                 |                  |
|-----------------|------------------|
| October 8, 1941 | 210/130          |
| “ 9, “          | 170/120; 210/120 |
| “ 10, “         | 170/120          |
| “ 11, “         | 130/110          |
| “ 12, “         | 140/110          |
| “ 13, “         | 130/100          |
| “ 14, “         | 140/100          |
| “ 15, “         | 150/106          |
| “ 16, “         | 155/110          |
| “ 17, “         | 130/ 70; 130/90  |
| “ 18, “         | 114/ 78          |
| “ 19, “         | 122/ 76          |
| “ 21, “         | 140/ 92          |
| “ 22, “         | 125/ 85          |

*Follow-up Record:* The headaches had not returned during the entire post-operative period except for an occasional mild frontal headache.

|           |          |                |           |
|-----------|----------|----------------|-----------|
| October   | 27, 1941 | Blood pressure | 130/ 86   |
| "         | 30, "    | "              | " 120/ 84 |
| November  | 6, "     | "              | " 130/ 90 |
| "         | 12, "    | "              | " 128/ 82 |
| January   | 6, 1942  | "              | " 142/104 |
| March     | 23, "    | "              | " 130/ 92 |
| May       | 8, "     | "              | " 142/100 |
| July      | 7, "     | "              | " 140/100 |
| September | 29, "    | "              | " 130/ 90 |
| November  | 24, "    | "              | " 132/ 90 |
| "         | 26, 1943 | "              | " 128/ 96 |

The patient states that he had an attack of coronary thrombosis 7 months previously.

|          |          |   |           |
|----------|----------|---|-----------|
| February | 10, 1944 | " | " 124/ 90 |
| October  | 24, "    | " | " 122/ 86 |

*Case 2. History:* L. K., male, aged 43 years, was admitted to The Mount Sinai Hospital on June 7, 1943.

In 1937 he suffered a left renal colic accompanied by gross hematuria. Since that time he had had recurrent lumbar back pain and hematuria. In 1941, during the course of a general physical examination, hypertension was noted. The systolic blood pressure fluctuated after going as high as 230 mm. of mercury. The minimum diastolic blood pressure had been 120 to 130. Since childhood he had suffered with headaches which of late became worse. Study of his various systems revealed nothing of note.

*Examination:* His eyes were normal. The fundi showed moderate arteriovenous compression and silvering of the arteries with an occasional small hemorrhage. The lungs were normal to auscultation and percussion. The heart was enlarged to the left. There were no murmurs. The aortic second sound was accentuated. The blood pressure was 180 systolic and 130 diastolic.

*Laboratory Data:* Urine clear; specific gravity 1020; albumin trace; sugar none; microscopic showed moderate number of red blood cells and a few white blood cells. Blood count: Hemoglobin 102 per cent; red and white blood cell counts were normal. Blood urea nitrogen 17 mg. per 100 cc. of blood.

*X-ray Examination:* The kidney outlines were normal in size, shape and position. There was a large calculus filling the pelvis and lower calices of the left kidney.

*Intravenous Pyelography:* The right kidney pelvis, calices and ureter were normal. The left kidney showed slight dilatation of the pelvis and moderate dilatation of the upper calices of the left kidney.

*Cystoscopy:* The bladder and ureter orifices were normal. Indigocarmine injected intravenously appeared in good concentration from the right kidney, and in only fair concentration from the left kidney.

*Electrocardiography:* Regular sinus rhythm. Left axis deviation. Q.R.S. of high voltage. R-1 and R-2 depressed. T-1 and T-2 diphasic and T-3 low. The changes indicated hypertrophy of the left ventricle with myocardial damage.

*Operation:* On June 17, 1943 (A. H.) a left lumbar nephrectomy was done.

The kidney was exposed through a left lumbar incision, and found surrounded by a thick fatty capsule which appeared to hold it in a vise. The renal pedicle was short. There was considerable perinephritis.

*Post-operative Course:* He made an uneventful convalescence and was discharged sixteen days after operation. The patient felt well, and during the post-operative hospital stay his blood pressures were recorded as follows:

|                   |   |
|-------------------|---|
| June 8, 1943..... | Blood pressure 230/150; 200/130<br>(preoperative) |
| " 17, " .....     | " " 140/ 98                                       |
| " 18, " .....     | " " 120/ 85                                       |
| " 19, " .....     | " " 150/100                                       |
| " 20, " .....     | " " 150/106                                       |
| " 21, " .....     | " " 148/100                                       |
| " 22, " .....     | " " 150/100                                       |
| " 23, " .....     | " " 150/100                                       |
| " 24, " .....     | " " 138/ 95                                       |
| " 26, " .....     | " " 130/ 80                                       |
| " 28, " .....     | " " 128/ 90                                       |
| " 30, " .....     | " " 105/ 75                                       |

*Pathology:* Calculus; Chronic Pyelonephritis. The kidney showed considerable arteriosclerosis as found in benign nephrosclerosis. The main branches of the renal artery showed marked arteriosclerosis with narrowing.

Chemical analysis of the renal calculus: Ammonium urates, calcium oxalate and ammonium magnesium phosphate.

*Follow-up Record:* Patient felt perfectly well since his discharge from the hospital. His only complaint was that he felt tired towards the end of the day. Until April 8, 1944 his blood pressure had been taken weekly, and averaged 130 systolic and 80 to 90 diastolic. The last blood pressure recorded was on October 3, 1944 as 134 systolic and 90 diastolic.

#### SUMMARY

In the numerous instances where nephrectomy was performed at this hospital in the presence of an associated essential hypertension, the above described cases stand out for the subjective and objective improvement in the previously present hypertension. The recorded late blood pressure readings are within normal range.

Several points are worth emphasizing. It is our belief that all patients with essential hypertension should have a urological examination consisting of an excretory urography and cystoscopic examination with renal function tests where unilateral disease is noted. It is difficult to tell pre-operatively which patients with essential hypertension and unilateral kidney disease will show improvement in the arterial tension following nephrectomy. Such an association does exist, but in our opinion and experience it is rather uncommon.

Until a more effective treatment of essential hypertension is discovered, we suggest the following empiric approach to the problem of unilateral renal disease combined with essential hypertension: Where a nephrectomy is decided upon for the existent nephropathy, a lumbar sympathectomy should be done at the same time on the side of the nephrectomy. If no improvement results, then a sympathectomy can be considered on the opposite side.

## GENERALIZED SECONDARY AMYLOIDOSIS

### A CLINICO-PATHOLOGICAL STUDY OF 84 CASES<sup>1</sup>

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Amyloidosis in human beings is considered to be an infrequent disease. This is partly due to the fact that it is often overlooked because of the presence of the primary disease. At The Montefiore Hospital for Chronic Diseases, amyloidosis was found in 7.2 per cent of a total of 1727 consecutive necropsies (1, 2). It was present in 24.4 per cent of all subjects with tuberculosis and in 44 per cent of all cases of tuberculosis with suppuration (3). At Seaview Hospital for Tuberculosis, New York, lardaceous disease in visceral organs was present in approximately 30 per cent of all tuberculous patients who were examined post mortem (4). In a series of 500 consecutive autopsies on adults in a general hospital (Beth-El Hospital), amyloid disease was found three times (0.6 per cent), in one instance clinically unsuspected. At the present time, tuberculosis is the most frequent primary disease responsible for the production of amyloidosis. Saleeby (5) found tuberculosis to be the underlying cause of amyloidosis in 82 per cent, Waldenstrom (6) in 93 per cent and Rosenblatt (1, 2) in 88 per cent of their cases. The present study is based on a study of 84 consecutive cases of amyloidosis complicating tuberculous or chronic suppurative disease.

Although the manifestations of amyloidosis vary considerably, secondary generalized amyloidosis presents a sufficient number of common pathological and clinical features, irrespective of those phenomena attributable to their primary causal factor, to warrant a general description of the disease. This is made possible by gathering the scattered clinico-pathological data in the literature and adding to these our own observations supported by some recent experimental studies. These experimental studies have changed our concept of the nature of the disturbance and manner of its development and progression, and have resulted in the use of a liver product as a therapeutic agent, which the authors have found to be of value in a group of patients suffering with this disease (7, 8, 9). Others have employed the same type of treatment and have reported similar clinical improvement (10-14). Experimental confirmation has been presented by Cavallucci (15).

*Etiology:* At least five theories are current. The allergy theory of Jaffee (16) and the "antigen-antibody union and precipitation" concept of Letterer (17, 18) and of others (19, 20) have little direct evidence in their favor. The same is true of the theory that the disease is exclusively a disorder of endogenous protein metabolism (21, 22). Recently the concept has been advanced (23, 24) that amyloidosis is due to an hyperproteinemia, more precisely, an hyperglobulinemia. The latter findings were present in some of our human cases but not in others.

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Hyperglobulinemia was absent in other reported cases (13, 25). These findings do not, however, explain the peculiar localization of amyloid in tissues found experimentally (7, 8b, 16, 18) or at autopsy. Finally, such a thesis does not suggest the reason for the protein changes and ignores the rôle of the reticular apparatus already shown experimentally (7, 8a, b, 16, 26).

The evidence which has accumulated favors the explanation that the disturbance is in the reticulo-endothelial system (26-29). The present authors and their colleagues, basing their views on the work of others, as well as on their own work (7, 8b) offered what appeared to them to be the most plausible theory, e.g., that amyloidosis is a disorder of endogenous protein metabolism in which the reticulo-endothelial system is involved (9).

Recent work by Hass (30) tends to show that amyloid substance, while a complex of proteins, has a structure similar to that of chondroitin-sulphuric acid obtained from infantile cartilage. This work, of a semi-quantitative nature, tends to confirm the much earlier work of Oddi (31) and Krakow (32), work subsequently questioned by Hanssen (33) and Eppinger (34). This study, however, sheds no new light on the etiology or pathogenetic mechanism of the disease.

While it is not yet possible to arrive at a final conclusion in regard to the mechanism of the production of amyloidosis, it seems possible to consolidate the last three explanations into one unified theory which may be summarized briefly as follows: A long continued infection or chronic wasting disease, or the introduction of a catabolism exciting agent, predisposes to excessive destruction of tissue protein. The disintegrated endogenous protein fractions cannot be readily metabolized or excreted by the body, and the reticulo-endothelial system is called upon to phagocytize these substances. At first it attempts to meet the situation by hypertrophy and hyperplasia. If the process of destruction continues, the reticulo-endothelial system decompensates, permitting increasing deposition of amyloid in the organs. Whether the hyperproteinemia or hyperglobulinemia is a manifestation of this disorder and is due to a general accumulation, or merely represents the transportation of the protein material from the source of origin to the endothelial system, is at present difficult to say. Indeed, there is as yet no evidence that globulin is the mother substance of amyloid. A somewhat similar concept for the pathogenesis of the so-called xanthomatous diseases has recently been advanced by Thannhauser and Magendantz (35). These authors go one step further for the xanthomatous diseases which, in many anatomical respects, are similar to amyloidosis. They suggest a disorder of intracellular lipid metabolism in the cells of the reticular system.

*Pathology:* Amyloidosis is a definite pathological entity characterized by the presence of a characteristic homogeneous protein material in various organs of the body, particularly the liver, spleen, and kidneys. Its exact chemical nature is not known. Analyses have shown it to consist of a variety of amino-acids, which vary qualitatively and quantitatively in different individuals and even in the same individual in different organs (30).

The deposition of amyloid is usually a secondary phenomenon following, as a rule, a prolonged suppurative infection or cachectic disease such as pulmonary or osseous tuberculosis, pulmonary abscess or bronchiectasis, chronic suppurative osteomyelitis, chronic

dysentery, syphilis, cancer with ulcerative lesions, chronic arthritis (13, 36), etc. It has been found as a primary generalized disease at autopsy without any evidences of inflammation or cachexia. This rare state, morphologically identical with secondary amyloidosis, is believed to be occasioned by excessive or improper protein metabolism (37), and is analogous to experimentally produced amyloid disease as produced by the feeding experiments of Kuczynski (22). With the continuance of the primary disease in the more frequent form of amyloid disease, progressive accumulation of lardaceous material occurs. More and more organs and tissues become sites for the deposition of this amyloid material; and the organs already involved become enlarged and contain an ever-increasing quantity of this substance. The increasing accumulation of this material interferes with the circulation within and the functions of the involved organs, eventually causing death of the infiltrated tissues. This process continues until there is such marked disturbance of vital functions of organs that the patient succumbs.

TABLE I  
*Age distribution of patients with amyloidosis*

| AGE IN YEARS | NUMBER OF CASES | PERCENTAGE OF TOTAL |
|--------------|-----------------|---------------------|
| 1-3          | 1               | 1.2                 |
| 3-5          | 12              | 14.8                |
| 5-10         | 9               | 11.8                |
| Under 10     | 22              | 27.1                |
| 10-15        | 8               | 9.9                 |
| 15-20        | 8               | 9.9                 |
| 10-20        | 16              | 19.8                |
| 20-30        | 28              | 34.6                |
| Under 30     | 66              | 81.5                |
| 30-40        | 7               | 8.7                 |
| 40-50        | 7               | 8.6                 |
| 51           | 1               | 1.2                 |
| Total.....   | 81              | 100.00              |

3 treated cases not included in this table (cases nos. 14, 15, 161, Table VII).

The pathology of amyloid disease has been the subject of much controversy. This is probably due to the fact that this disease in the human is ordinarily seen at comparatively late stages in clinical cases and at a much later stage at autopsy. The experimental production of the disease by Birch-Hirschfeld (38), in 1882 aided in an understanding of its morbid anatomy. His successful production of generalized amyloidosis in a dog injected subcutaneously with pus from a case of bone caries, was confirmed by Charrin (40) several years later. Amyloid disease has since been produced by the injection of pyogenic organisms (41-43), pus (44), or even inorganic substance (17); and Kuczynski (22) produced it by feeding mice a diet rich in proteins.

The next advance which contributed much to our understanding of the pathology of the disease was the finding of a new tinctorial method for the demonstration of amyloid in an earlier stage than had previously been possible with violet dyes. Although crystalline forms of amyloid had been reported earlier by Schuster, Schmidt, Lubarsch and Maximow (21), it was Bennhold (45) who first used Congo red to demonstrate early amyloid in tissue. Smetana (46) employing Congo red intravital demonstrated deposits of amyloid within cells of the reticulo-endothelial system. Jaffee (16) used it to demonstrate amyloid in the Kupfer cells lining the sinusoids of the liver; and we (7, 8b) employed it to stain amyloid in the spleen and liver and noted similar intracellular inclusions in the kidney. In addition,

it enabled us to demonstrate the transition of amyloid from the intracellular to the extracellular phase.

These two approaches to the problem of amyloidosis made possible the reconstruction of the earliest objective pathological findings and the progressive developmental changes of amyloidosis in the human organs. That the transformations noted in lower animals closely approximate those found in the human beings is justified from the fact that in both the end stages are identical in appearance, distribution, localization, and chemical and staining properties of the material. The earliest findings are those of hypertrophy and hyperplasia of the fixed and wandering cells of the reticulo-endothelial system. This is followed by the appearance of characteristic pink or red inclusion masses of amyloid in the fixed and wandering macrophages, which may be detected by the intravenous administration of a one per cent aqueous solution of Congo red shortly before death. The intracellular substance is at first crystalline in appearance and is radially arranged. This morphologic stage has not yet been seen in human cases. Later it becomes homogeneous and occupies more and more of the cytoplasmic area. The phagocytic cells become enlarged and soon two or more fuse to form giant cells. These ultimately disintegrate and amyloid begins to be deposited in the extracellular spaces. The amyloid is laid down as a shell around reticulum fibers. This process continues until the accumulation of the lardaceous substance is widespread, i.e. the typical picture seen at autopsy (8b).

There are, of course, marked variations in the extent and degree of amyloid change in different cases. The initial seat of the deposit and the order in which the different organs are affected also vary with the individual case and are not apparently related to the character of the primary disease. In most cases the liver, the spleen, or kidney, organs containing relatively large numbers of reticulum cells, are the ones usually affected. In the usual advanced cases, as in our series, other organs, in addition to the three mentioned above, present marked amyloid deposition. The organs are generally swollen and show an increase in weight, volume and consistency. They are hard and inelastic, pale and light buff gray or brown in color, because of the diminution of blood supply.

Microscopically, amyloid appears as a homogeneous, highly refractive substance which is deposited, as Ribbert (47) put it "primarily, in its narrowest sense, in the vascular apparatus. The substance is deposited on the outer surface of capillaries, in the muscularis of arteries, and in the intima of veins, but further also in the fibers of connective tissue, in tissue spaces, and lies free within lymph channels. On the other hand, the functional cells of the various organs, such as the liver cells, the renal epithelium, the lymph nodules, and the connective tissue cells are never the seat of amyloid change. These latter can only be infiltrated by amyloid when they have died and disintegrated." It is interesting to note the close parallelism of the sites of amyloid deposit described by Ribbert and the location of the reticulum cells capable of phagocytosis (48). In advanced stages, owing to the increasing accumulation of this material and to the atrophy of the surrounding tissues, the masses of amyloid increase in size and become confluent, so that, the entire organ, or a large part of it, may be replaced by amyloid.

The specific staining reactions of amyloid are characteristic. With iodine, the cut surface assumes a deep mahogany color which changes to brownish blue black upon the addition of dilute sulphuric acid. Microscopically, the homogeneous lardaceous material may be differentiated from normal tissues by the brownish-blue or blue-black color which it presents on treatment with Lugol's solution when followed by dilute sulphuric acid. With methyl violet amyloid assumes a rose or deep red color, as contrasted with the blue of the surrounding tissue.

Amyloid has been found in the heart, blood vessels, connective and adipose tissue, the larynx, bronchi, spleen, lymph nodes, bone marrow (both flat and long bones), the kidneys, adrenals, ureters, bladder, uterus, ovaries, tongue, pharyngeal wall, esophagus, stomach, intestines, pancreas, salivary glands, thyroid, striated muscle, including those of the diaphragm, the skin, and the eye (49). The identity of the so-called amyloid bodies in the central nervous system with amyloid material found in other organs is still a matter for

dispute (50). The organs most frequently involved are as already mentioned, the spleen, the liver, the lymph nodes, and the kidneys, in the order named. These will be described more fully.

The *spleen* is enlarged, often to a very marked degree. It is much firmer than usual, is often of a ligneous consistency, and can only be cut with considerable difficulty. The cut surface is smooth, shiny, transparent, and of a light buff gray or brown color. In less extensively involved organs, the amyloid appears as a concentric homogeneous cellular ring (sago form) of varying width, surrounding a compressed, distorted, or atrophic follicle. In the form described as resembling cooked bacon the homogeneous amyloid appears in the red pulp as a lattice of strands of varying width, which seemingly line the apparently narrowed and bloodless pulp sinuses. Amyloid rings, usually narrower and less complete than in the sago-type, may also surround the follicles. In both forms the trabeculae are thickened, and the homogeneous amyloid is present within the trabeculae, chiefly around the thickened arteries or lying within their walls.

The *liver* is markedly enlarged, voluminous, firm, and rubbery and is cut with great difficulty. The surface is smooth, pale, light buff gray in color, dry, transparent and shiny; the capsule is transparent and is usually not thickened. On section, the lobules are not altered or they may be atrophic. Histologically, in sections showing early stages of the disease, a stage rarely encountered in human beings, the amyloid is seen in the walls of the arteries of the portal spaces, but more often it appears as a narrow band of homogeneous acellular substance between the Kupfer cells and the adjacent liver cord cells. This deposit is usually first seen in the midzonal region, later spreading centrally and peripherally. As the amounts of the amyloid deposit increase, the cords disappear entirely. In the latter stages the tubes (capillaries) appear empty and are surrounded by a dense, acellular substance in which are seen remnants of liver cells, without definite arrangement, and a few areas suggesting a pre-existing portal space.

The *kidneys*, until the very late stages when a secondary contraction may occur, are moderately enlarged. They are firmer than usual, the capsule is smooth and easily removed but is not as tense as in the normal state. They are more resistant to cutting and more rubbery than usual, but not nearly to the same degree as are the spleen and the liver. The medulla is usually somewhat firmer than the cortex. The cut surface is smooth and shiny in appearance. The glomeruli stand out prominently as transparent, gray, glassy nodules in the cortex. The walls of the arcuate arteries are generally somewhat thicker and more prominent than usual, and the entire organ may be somewhat anemic. These findings are not, however, very striking.

Histologically, the amyloid first appears in the kidneys as droplet collections of homogeneous, glassy, transparent acellular substance in the membrana propria of the vessels, especially the afferent and efferent arterioles, the venae rectae, and glomerular and cortical capillaries. They are found less frequently in the membrana propria of the tubules, especially those of the convoluted tubules; and even less often in Henle's loop, the collecting tubules, and Bowman's capsule. The latter are usually involved only in the late stages of the disease, when the glomerulus is infiltrated with amyloid, the tuft is enlarged and the capillary lumen is narrowed or obliterated, so that the renal corpuscle is converted into a bloodless homogeneous mass, completely filling the capsular space and containing nuclear debris, the remains of the endothelial and epithelial cells. Because of the accumulation of amyloid around the tubules, these appear narrowed and lined by epithelial cells in varying stages of necrobiosis, from fatty changes to complete necrosis and desquamation. In the interstitial tissue, the amyloid appears chiefly around arteries and capillaries, or in the arterial walls, and less frequently in the interstitial connective tissue reticulum remote from blood vessels. The interstitial tissue may, however, present an inflammatory cellular reaction, which in the late stages of the disease is transformed into fibrous scars, causing contraction of the entire organ.

The *other organs* less frequently involved show only slight amyloid changes. In the *intestines* the infiltration is widespread but patchy. The entire wall may be thickened and

firm, or the intestinal folds alone may appear thicker, wider, and stiffer than usual. The heart, when involved, may be normal in gross appearance or may be slightly enlarged. On section it usually assumes a diffuse yellowish red appearance. Amyloid deposition in the myocardium is rare, but may occur in the endocardium, especially in the right auricle. The adrenals when involved, are thickened and quite firm, and the cut surface appears homogeneously gray. The amyloid is usually found in the cortex, which it may replace nearly completely. It is to be emphasized that the location and amount of amyloid parallels closely that of the cells of the reticulo-endothelial system of the organ in question.

#### CLINICAL ANALYSIS

The present study consists of a clinical analysis of eighty-four consecutive and definitely proven cases of untreated moderately advanced and advanced amyloidosis. Sixty-one of these were examined post mortem; all showed definite pathological evidence of amyloidosis. The remaining twenty cases had all the symptoms and signs of lardaceous disease, including positive Congo red tests (90 to 100 per cent retention). These cases will be contrasted later with 16 treated cases.

TABLE II  
*Sex distribution of patients with amyloidosis*

| SEX         | NUMBER OF CASES | PERCENTAGE OF TOTAL |
|-------------|-----------------|---------------------|
| Female..... | 28              | 34.5                |
| Male.....   | 53              | 65.5                |

3 treated cases (nos. 14, 15, 16, Table VII) not included in this table.

*Age Distribution:* It is a well known fact that tuberculosis, and particularly bone tuberculosis, usually begins in the earlier period of life. The activity and malignancy of general tuberculosis appears also to be more pronounced in this same age period. Since amyloidosis is usually a secondary phenomenon of the more persistent infections, it occurs more often in this early age group. This is illustrated in Table I which shows an incidence of 22, 16 and 18 cases, respectively (approximately 82 per cent of all the subjects) during the first, second and third decades of life.

*Sex Distribution:* Amyloidosis also bears a close parallel to the sex incidence and severity of tuberculous infection. As in tuberculous infection in general males are more frequently and much more severely affected than females, so in our experience with amyloidosis the male subjects, when first seen, usually presented later stages of the tuberculous infection and of amyloidosis than did the female patients. In the present series about 66 per cent were males (Table II).

#### RELATIONSHIP OF PRIMARY TUBERCULOUS INFECTION TO AMYLOIDOSIS

a. *Nature and Distribution of the Primary Infection:* In the present series of cases, amyloidosis was a complicating factor in pulmonary and bone tuberculosis and was absent in cases of tuberculosis of the skin, eyes, ears, kidneys, and glands alone, although patients affected with infections of these organs were present in the institutions in which this study was made. The pulmonary lesions were all of the caseous and necrotizing type, and the bone infections involved chiefly the spine, hip and knee. Other sites of bone infection were rarely associated with amyloidosis. In the present study, 31 patients (38.3 per cent) had pulmonary tuberculosis alone as the primary illness, and 37 (45.7 per cent) suffered from bone tuberculosis. The remaining 13 patients (16.0 per cent) had combined lesions (Table III). Although it is difficult to estimate very accurately the relative incidence of pulmonary phthisis as compared with bone tuberculosis in a population in general, there is no question that the pulmonary type predominates. Thus in a report (51) representing



a total of 89,237 patients in 494 institutions, 87 per cent were of the pulmonary type, 8.7 per cent of the childhood type, and 4.3 per cent of the non-pulmonary forms, and in a report from The New York Tuberculosis and Health Association (1933) the incidence of pulmonary tuberculosis is given as 12.8 times that of the non-pulmonary forms. If the incidence of amyloidosis were equal in pulmonary and in bone tuberculosis, one would expect a much greater number of patients with pulmonary tuberculosis to be affected with amyloidosis. This however was not the case in our series. On the contrary the incidence was greater in the non-pulmonary group. This would seem to indicate that although pulmonary phthisis is very much more frequent than bone tuberculosis, amyloidosis occurs very much more often in the latter type of infection. This relationship may only apply in institutions having advanced forms of both types of tuberculous disease.

b. *Duration of the Primary Disease before the Onset of Amyloidosis (Table IV):* Sixty-four patients (80 per cent) had the initial infection for 5 years or less. Of the pulmonary cases, 19 or 61 per cent had the disease for 3 years or less; and 27 or 87 per cent, for one to

TABLE III

*Nature and distribution of primary tuberculous infection leading to amyloidosis*

| SITE OF PRIMARY INFECTION                        | NO. OF CASES | PERCENTAGE |
|--|--------------|------------|
| Pulmonary.....                                   | 31           | 38.3       |
| Spine.....                                       | 15           | 18.6       |
| Hip (ilium and femur involved).....              | 12           | 14.9       |
| Pulmonary and spine.....                         | 8            | 9.9        |
| Knee.....  | 5            | 6.2        |
| Spine and hip.....                               | 2            | 2.5        |
| Pulmonary and hip.....                           | 1            | 1.2        |
| Pulmonary, hip and ankle.....                    | 1            | 1.2        |
| Pulmonary and tuberculous peritonitis.....       | 1            | 1.2        |
| Pulmonary and suppurative cervical adenitis..... | 1            | 1.2        |
| Spine, ribs and ankle.....                       | 1            | 1.2        |
| Spine and suppurative cervical adenitis.....     | 1            | 1.2        |
| Shoulder and elbow.....                          | 1            | 1.2        |
| Shoulder and knee.....                           | 1            | 1.2        |
| Total.....                                       | 81           | 100.00     |

3 treated cases (nos. 14, 15, 16, Table VII) not included in this table.

five years. In the bone group, on the other hand, 21 persons (57 per cent) had the primary illness for one to three years; and 28 (75 per cent), for one to five years. This apparent "time difference" between the pulmonary and bone groups seemed to predominate in the hip infections. One-fourth of the total number of cases with hip involvements had the primary disease from one to three years, and one-half within five years; and in the remaining one-half, the amyloidosis occurred after five years of the initial infection. On the other hand, in knee and spine tuberculosis the occurrence of amyloidosis within five years of the primary infection was 100 and 86 per cent, respectively. Amyloidosis, therefore, occurs relatively infrequently after the fifth year of a tuberculous infection, and is apparently uncommon in those having a comparatively mild relapsing type of tuberculosis. In such instances the active infection is of relatively short duration and is interrupted by significant periods of quiescence or inactivity. On the other hand, the more severe forms of the primary disease with persistently long periods of activity, are the more apt to acquire the lardaceous complication within three years. In those cases in which amyloidosis occurred after an interval longer than three years following the onset of tuberculosis, the

initial infection was at first of a milder nature but became severe with the next or succeeding relapses.

Using the appearance of albuminuria in proved cases of amyloidosis complicating tuberculosis as the index of appearance of the amyloid complication, Cohen (25) arrives at an average duration of 64.2 months between the onset of the initial disease and the amyloid complication. This figure agrees rather closely with ours.

TABLE IV

*Duration of primary disease according to site, before the onset of amyloidosis*

Number of cases, grouped according to duration of tuberculosis before appearance of amyloid

| Location of Primary diseases          | 1 yr. | 2 yrs. | 3 yrs. | 4 yrs. | 5 yrs. | 6 yrs. | 7 yrs. | 8 yrs. | 9 yrs. | 10 yrs. | 10-15 yrs. | 15-20 yrs. | 20-25 yrs. | 25-30 yrs. | 30-40 yrs. | NO. OF CASES |
|---------------------------------------|-------|--------|--------|--------|--------|--------|--------|--------|--------|---------|------------|------------|------------|------------|------------|--------------|
| Pulmonary . . . .                     |       | 8      | 11     | 4      | 4      | 1      | 1      | 1      |        | 1       |            |            |            |            |            | 31           |
| Pulmonary and spine . . . . .         |       | 4      | 2      |        |        |        |        | 1      | 1      |         |            |            |            |            |            | 8            |
| Pulmonary and hip . . . .             |       | 1      |        |        |        |        |        |        |        |         |            |            |            |            |            | 1            |
| Pulmonary, hip and ankle . . . .      |       |        |        | 1      |        |        |        |        |        |         |            |            |            |            |            | 1            |
| Pulmonary and peritoneum . . . . .    |       |        |        |        |        | 1      |        |        |        |         |            |            |            |            |            | 1            |
| Pulmonary and cervical . . . . .      | 1     |        |        |        |        |        |        |        |        |         |            |            |            |            |            | 1            |
| Spine . . . . .                       | 1     | 8      | 2      |        | 2      |        | 1      | 1      |        |         |            |            |            |            |            | 15           |
| Spine and hip . . . . .               |       |        |        |        |        |        |        |        | 1      |         |            | 1          |            |            |            | 2            |
| Spine, ribs, and left ankle . . . .   |       | 1      |        |        |        |        |        |        |        |         |            |            |            |            |            | 1            |
| Spine and glands (cervical) . . . . . |       | 1      |        |        |        |        |        |        |        |         |            |            |            |            |            | 1            |
| Hip (femur and ileum) . . . . .       | 1     | 4      |        |        | 1      | 1      |        |        | 2      | 1       |            |            | 1          |            | 1          | 12           |
| Pulmonary and knee . . . . .          |       | 3      | 1      |        | 1      |        |        |        |        |         |            |            |            |            |            | 5            |
| Knee and shoulder . . . . .           |       |        | 1      |        |        |        |        |        |        |         |            |            |            |            |            | 1            |
| Shoulder and elbow . . . . .          |       |        |        | 1      |        |        |        |        |        |         |            |            |            |            |            | 1            |
| Total . . . . .                       | 3     | 30     | 17     | 6      | 8      | 3      | 2      | 3      | 4      | 2       |            | 1          | 1          |            | 1          | 81           |

Percentage. } 61.7 per cent within 3 years  
79.1 per cent within 5 years

3 treated cases (nos. 14, 15, 16, Table VII) not included in this table.

*c. Duration of Discharging Sinuses before the Onset of Amyloidosis:* Of the 81 cases with amyloid, 52 had discharging sinuses. All those with tuberculous bone infections, numbering 48 in this series, developed one or more sinuses. Of the remaining four, there were three with pulmonary tuberculosis, and one with pulmonary and peritoneal tuberculous disease. The sinuses in these four cases followed a surgical procedure with resulting discharging wound. The sinuses were all present for varying periods of time before the onset of amyloi-

TABLE V

*Duration of discharging sinuses before the onset of amyloidosis*

| LOCATION OF DISCHARGING SINUSES | NUMBER OF CASES GROUPED ACCORDING TO DURATION |       |         |        |         |        | NO. OF CASES |
|---------------------------------|---|-------|---------|--------|---------|--------|--------------|
|                                 | 6 mos.  | 1 yr. | 1½ yrs. | 2 yrs. | 2½ yrs. | 3 yrs. |              |
| Pulmonary.....                  |   | 1     | 1       | 1      |         |        | 3            |
| Pulmonary and spine.....        | 1   | 5     |         |        |         | 2      | 8            |
| Pulmonary and hip.....          |   |       | 1       |        |         |        | 1            |
| Pulmonary, hip and ankle.....   |   |       |         | 1      |         |        | 1            |
| Pulmonary and peritoneum.....   |   |       |         | 1      |         |        | 1            |
| Spine.....                      | 1   | 7     | 6       |        | 1       |        | 15           |
| Spine and hip.....              | 1   |       |         |        |         | 1      | 2            |
| Spine, ribs and left ankle..... |   | 1     |         |        |         |        | 1            |
| Spine and cervical glands.....  |   |       | 1       |        |         |        | 1            |
| Hip.....                        |   | 4     |         | 5      | 1       | 2      | 12           |
| Knee.....                       |   | 1     |         | 3      |         | 1      | 5            |
| Knee and shoulder.....          |   |       |         |        | 1       |        | 1            |
| Shoulder and elbow.....         |   |       |         |        |         | 1      | 1            |
| Total.....                      | 3   | 19    | 9       | 11     | 3       | 7      | 52           |
| Percentage.....                 | 80.76 per cent within 2 years                 |       |         |        |         |        |              |

TABLE VI

*Duration of amyloidosis in untreated cases  
(to time of death)*

| LOCATION OF PRIMARY DISEASE        | NO. OF CASES GROUPED ACCORDING TO DURATION                      |       |         |        |        | TOTAL |
|------------------------------------|---|-------|---------|--------|--------|-------|
|                                    | 6 mos.  | 1 yr. | 1½ yrs. | 2 yrs. | 3 yrs. |       |
| Duration.....                      |   |       |         |        |        |       |
| Pulmonary.....                     |   | 28    | 1       | 1      | 1      | 31    |
| Pulmonary and spine.....           | 1   | 6     | 1       |        |        | 8     |
| Pulmonary and hip.....             |   | 1     |         |        |        | 1     |
| Pulmonary, hip and ankle.....      |   | 1     |         |        |        | 1     |
| Pulmonary and peritoneum.....      |   | 1     |         |        |        | 1     |
| Pulmonary and cervical glands..... |   |       |         | 1      |        | 1     |
| Spine.....                         |   | 8     | 1       | 2      | 1      | 12    |
| Spine and hip.....                 |   | 1     |         |        |        | 1     |
| Spine, ribs and left ankle.....    |   | 1     |         |        |        | 1     |
| Spine and cervical glands.....     |   | 1     |         |        |        | 1     |
| Hip.....                           |   | 1     | 3       | 2      |        | 6     |
| Knee.....                          | 1   | 2     |         |        |        | 3     |
| Shoulder and elbow.....            |   | 1     |         |        |        | 1     |
| Total.....                         | 2   | 52    | 6       | 6      | 2      | 68    |
| Percentage.....                    | 79.41 per cent within 1½ years<br>97.58 per cent within 2 years |       |         |        |        |       |

dosis, the maximum duration of the suppurative process before the appearance of evident amyloidosis being three years. In 80 per cent of the cases, amyloidosis appeared within 2 years after the appearance of a sinus (Table V). When compared with the general dura-

TABLE VII  
Summary of results with liver therapy in secondary amyloidosis\*

| CASE | AGE AT ONSET OF PRIMARY DISEASE | DURATION OF 1° DISEASE TO TIME OF APPEARANCE OF AMYLOID | DURATION OF 1° DISEASE AFTER ONSET OF AMYLOID | AGE AT ONSET OF AMYLOID | DURATION OF AMYLOID BEFORE TREATMENT | DURATION OF AMYLOID DURING TREATMENT | RESULTS OF LIVER THERAPY OF AMYLOID | REMARKS  |
|------|---------------------------------|---|---|-------------------------|--------------------------------------|--------------------------------------|-------------------------------------|--|
| 1    | 7                               | 4 yrs.  | 14 yrs.                                       | 11 yrs.                 | 3 yrs.                               | 2 yrs.                               | Cured                               | Tbc. active for 6 yrs. after disappearance of amyloid. Albuminuria still present (trace). Congo red no retention at present.   |
| 2    | 7½                              | 2   | 8   | 9                       | 1½                                   | 2                                    | Cured                               | Tbc. active for 4 yrs. after disappearance of amyloid. No albuminuria or Congo red retention at present.   |
| 3    | 3½                              | 2½  | 3½  | 6                       | 1½                                   | 1½                                   | Died                                | Liver therapy taken poorly and irregularly.  |
| 4    | 6 (?)                           | 1 (?)   | 3   | 7                       | 2½                                   | ½                                    | Died                                |  |
| 5    | 7½                              | 1½  | 4½  | 9                       | ½                                    | 3½                                   | Died                                | Left hospital after 2½ yrs. treatment, at which time showed clinical evidence of improvement and Congo red retention had been reduced to 50%. Tbc. still active at discharge. Had no therapy for last 8 mths. of life. |
| 6    | 7                               | 2½  | 9   | 9½                      | 2                                    | 1½                                   | Cured                               | Tbc. active for 5 yrs. after disappearance of amyloid. No albuminuria or congo red retention at present.   |
| 7    | 2½                              | 1   | 12½   | 3½                      | 1½                                   | 2                                    | Cured                               | Tbc. active for 6 yrs. after disappearance of amyloid. One plus albuminuria, moderate casts still present. No Congo red retention at present.  |
| 8    | 7½                              | 2½  | 9½  | 10                      | ?                                    | 3                                    | Cured                               | Infection active, with new foci, for 4 yrs. after disappearance of amyloid. Albuminuria (trace) still present. No congo red retention at present.  |
| 9    | 3                               | 2½  | 12  | 5½                      | ½                                    | 7                                    | Cured                               | Tbc. active for 4 years after disappearance of amyloid. No albuminuria or congo red retention at present.  |
| 10   | 4                               | 4½  | 8½  | 8½                      | ½                                    | 4½                                   | Cured                               | Tbc. active for 4 yrs. after disappearance of amyloid. No albuminuria or congo red retention at present.   |

|    |          |                              |          |    |     |                                    |              |                     |   |
|----|----------|------------------------------|----------|----|-----|------------------------------------|--------------|---------------------|---|
| 11 | 7        | Tbc. hip                     | 3½       | 9  | 10½ | 3                                  | 6            | Cured               | Tbc. active for 2 yrs. after disappearance of amyloid. Two plus albuminuria, few casts still present. No Congo red retention.   |
| 12 | 9        | Tbc. hip                     | 1        | 2½ | 10  | 4                                  | 2½           | Died                | Took liver therapy poorly and irregularly, in total about 7 months equivalent therapy.  |
| 13 | 8        | Tbc. hip                     | 3        | 2  | 11  | 3                                  | 1½           | Condition unchanged | Took liver therapy irregularly. Discharged against advice, no response to follow-up.  |
| 14 | 17       | Chronic spinal osteomyelitis | 6        | 6  | 23  | 2                                  | Irregular, 6 | Improved            | Relapses in amyloid clinical picture with cessation of liver therapy. Chronic bone disease still active. Congo red retention 56%, moderate albuminuria at present.  |
| 15 | 9        | Tbc. hip                     | 2        | 3½ | 11  | 4                                  | 1½           | Cured               | Tbc. active for 20 months after disappearance of amyloid, at which time hip fusion was performed. Sinuses persisted 9 months after fusion. No congo red retention, slight albuminuria, occasional cast present at time of fusion. Tbc. now quiescent. |
| 16 | about 11 | Tbc. spine                   | About 3½ | 4½ | 14½ | Unknown; A. advanced when admitted | About 2      | Improved markedly   | Tbc. active 2½ yrs. after improvement in amyloid state; spleen palpable 1 f., liver 1 f. (from 9 and 7 cm. respectively). Albuminuria 2 plus, frequent casts, congo red retention of 60% still present.   |

\* All the cases in this series showed 100% Congo red retention. Albuminuria 4 plus, and many casts in urine when liver therapy was begun. For earlier case details (cases 1 to 13) see Ann. Int. Med. 12: 39 (1938).



tion of the primary disease before the onset of amyloidosis (see b) (in which 80 per cent occurred within five years), it is evident that the existence of discharging sinuses tends to accelerate the development of the lardaceous condition.

d. *Duration of Amyloidosis (Tables VI & VII):*

All of the cases of amyloidosis treated according to usual surgical and medical procedures in this series died. Of the 68 patients in the group, the majority died within one year after the onset of definite clinical symptoms of amyloidosis, and practically all succumbed within 2 years (Table VI). It may be that the disease existed for a longer period than our data indicate, an error attributable to delay in recognizing the complicating disease. These cases were all seen by the same group of men so that the error if present, probably is not of greater magnitude than one-half year. Cohen (25) similarly found that 88 per cent of his 79 amyloid patients died within 2 years after the development of amyloidosis, and Pearlman (52) that 92 per cent of 135 cases had died within a similar interval. The 16 individuals who, in addition to the usual therapy, received desiccated powdered whole liver, followed an entirely different course. Even those who died (4 patients) lived for 3 years with amyloidosis. The others are still alive after varying periods of time, ranging from 8 to 14 years after the onset of amyloidosis (see Table VII). More will be said of this specially treated group in a later portion of this paper.

SIGNS AND SYMPTOMS

The clinical features of secondary amyloidosis may vary considerably. This is due to the fact that both the primary inciting disease and its secondary complication of lardaceous disease, are present at the same time and each contributes to the symptomatology. The clinical picture will depend, therefore, upon the site, nature, extent and degree of severity of the primary illness as well as of the secondary amyloidosis.

The clinical picture and course of a patient with amyloidosis generally present, however, a fairly well defined pattern of symptoms. Amyloidosis is first preceded by a train of symptoms caused by the primary illness. Without entering into any detailed description of the particular symptoms of the initial disease, brief mention may be made of the common general symptoms which herald the onset of the lardaceous complication. At first the subject presents the usual characteristics of chronic and long standing disease, e.g., pallor, some loss of weight, weakness and poor appetite. Very occasionally there is a slight increase in weight, in some instances associated with the early onset of ascites. It has been our observation that at about the time of onset of amyloid changes there occurs an apparent aggravation of symptoms of the inciting tuberculous disease, especially in the febrile state. Whether or not these phenomena are causally related is unknown. As the condition progresses, a more rapid increase in these symptoms occurs. In place of pallor, a pasty or waxy color appears; the wasting and cachexia, unless obscured by dropsy, are characterized by marked loss of subcutaneous fat in the extremities, in face and thoracic region, as well as by poor muscular tone and flabbiness. The abdomen enlarges due to the increase in size of the liver and spleen. The superficial abdominal and thoracic veins become prominent and later markedly dilated and tortuous. The liver and spleen usually become increasingly large and firm, at times reaching the level of the umbilicus within 3 to 12 months. In a large number of cases, the lower hepatic edge extends below the crest of the ilium. The liver in the later stages enlarges much more rapidly than the spleen. The hepatomegaly and splenomegaly with or without ascites cause a markedly protuberant abdomen. Edema of the feet and legs may occur at any stage of the disease, though it is more often seen in the advanced state. In some instances dropsy becomes so marked that the transudate occurs in the penis, scrotal sac and pleural cavities.

The above description is the usual one and occurs in subjects in whom generalized amyloidosis develops relatively slowly and over a long period. There are however numerous variations in the clinical features depending on the organs chiefly affected and the degree of involvement. For example the kidney may be the only one affected or the only one showing significant changes and clinical symptoms. To obtain a clearer picture a more detailed study is desirable.

*Liver and Spleen:* It is exceptional for the seat of amyloidosis to be limited to the liver. Infrequently splenic or renal amyloidosis of the secondary type may be present without a lardaceous liver; in most instances hepatic involvement is present and extensive. In our series, 77 of the 81 cases showed hepatomegaly and all were associated with splenomegaly. This splenic enlargement was occasioned, as was the hepatomegaly, by amyloid deposition within the organ and not merely as the result of stasis due to hepatic changes. The liver is uniformly enlarged, smooth and firm. The lardaceous spleen is usually definitely enlarged although in a few instances it was only just palpable. In about 60 per cent of the cases the spleen extended to or below the level of the umbilicus. Although the amyloid liver or spleen usually produces no pain and tenderness, there were a few exceptions in our series.

*Abdomen:* Meteorism, which is often present, aggravates the abdominal enlargement. Further enlargement occurs in the presence of ascites. If fluid accumulates rapidly, the abdomen becomes markedly globular. With slower transudation, it becomes uniformly distended with bulging of the flanks.

*Extracellular transudation:* In 37 (45.67 per cent) of our cases, there was no extracellular transudation even at the time of death. In the remainder it usually occurred shortly before death. When present in the earlier stages of the disease, it consisted, as a rule, of swelling of the feet which slowly extended to the legs. Forty-four cases showed edema of the feet, forty-two of the lower extremities. Only 8 subjects had edema of the face.

Ascites occurred in 31 instances. In each case there was marked hepatosplenomegaly. Nine showed evidence of ascites fairly early in the disease. Ascites is very often disproportionate to edema elsewhere. Generalized anasarca was recorded in only 8 of our cases and hydrothorax in 6. Edema of the extremities and face may give a false impression of good nutrition.

Lowered serum protein and renal impairment are probably the two most common causes responsible for the edema. Cardiac decompensation may play a role in the terminal stages. Ascites and hydrothorax may be caused entirely or in part by the localized circulatory disturbance due to the extensive hepatic and splenic involvement.

*Gastro-Intestinal:* Anorexia is fairly common. Short periods of nausea and vomiting with or without abdominal pain or bowel disturbance frequently occur. Blood may be present in the vomitus or stool. Except in cases of tuberculous enteritis, all these symptoms, including diarrhea, were not very striking or prolonged.

*Heart:* The majority of our patients showed no significant cardiac signs or symptoms. The heart was of normal size; the heart sounds were of poor quality. There were no organic murmurs. In 6 instances pericarditis with or without effusion was observed. In these cases the heart was enlarged and there were, in addition to the occasional finding of a friction rub, systolic and diastolic murmurs. No electrocardiographic studies were available.

Blood pressure readings were within normal limits or slightly subnormal. In only a few cases was it slightly or moderately elevated; in the latter there was definite evidence of renal impairment.

*Adrenals:* Of 18 cases of amyloidosis secondary to tuberculosis, Bronfin and Guttman (53) found the cortex of the adrenals involved in 14 patients. In 5 of these subjects the symptoms of Addison's disease were noted during life. In the others some of the symptoms such as debility, hypotension, etc., may have been due to adrenal insufficiency. None of our cases showed clinical evidence of Addison's syndrome, although 12 cases showed amyloid involvement of the adrenals at post mortem.

*Eyegrounds:* The optic disks and retinæ were normal in 20 cases examined. This is in accordance with observations of other authors (54, 55).

*Renal and Urinary Symptoms:* This aspect of amyloidosis has received the most attention (1, 54-56). Renal amyloidosis frequently occurs in cases of generalized amyloidosis. On the other hand lardaceous disease of the kidneys may be present alone.

Albuminuria in the presence of generalized lardaceous disease does not necessarily indicate renal amyloidosis (1, 5, 13). Conversely, renal amyloidosis may be present without the presence of albumin, casts or other cellular elements in the urine (57). The more

common picture of generalized amyloidosis is one involving the kidneys and presenting moderate to marked albuminuria. The albumen in the urine may vary from a slight amount to a very large quantity. The urine may boil solid. As much as 3 to 10 gm. of albumen per liter may be excreted daily but the quantitative output varies considerably even in individual cases. In instances where slight amounts of albumen were obtained, there were days when no albumen was found upon qualitative examination. Albuminuria usually preceded any other pathological urinary finding by several months. At times it was present

## Chemical studies of c

| PATIENT .....                  | J       | A       | H       | M       | He      | N       | C. C.   |         | E. L.  |         |         |          |    |
|--------------------------------|---------|---------|---------|---------|---------|---------|---------|---------|--------|---------|---------|----------|----|
| Date                           | 8/21/34 | 8/21/34 | 8/21/34 | 9/15/34 | 9/15/34 | 9/24/34 | 9/24/35 | 9/22/36 | 2/7/30 | 2/19/31 | 9/24/34 | 10/15/35 | 8/ |
| Condition of amyloidosis ..... | +++     | ++++    | ++++    | ++++    | +++++   | +++     | ++++    | +++     | +++    | 0       | 0       | 0        |    |
| Total nitrogen (mgm. %)        | 1155    | 1115    | 1025    | 960     | 755     | 1105    | 983     | 1012    | 829    | 867     | 958     | 1123     | 1  |
| N.P.N. (mgm. %)                | 39      | 32      | 41      | 22      | 64      | 33      | 40      | 35      | 36     | 21      | 29      | 30       |    |
| Total protein (%)              | 6.96    | 6.76    | 6.138   | 5.87    | 4.30    | 6.69    | 5.89    | 6.11    | 5.02   | 5.29    | 5.81    | 6.83     |    |
| Albumin (%)                    | 3.06    | 1.71    | 0.688   | 2.46    | 1.18    | 2.44    | 2.30    | 2.23    | 1.74   | 2.28    | 2.48    | 3.94     |    |
| Globulin (%)                   | 3.90    | 5.05    | 5.45    | 3.41    | 3.12    | 4.15    | 3.59    | 3.88    | 3.28   | 3.01    | 3.33    | 2.89     |    |
| A/G .....                      | 0.785   | 0.34    | 0.126   | 0.72    | 0.38    | 0.61    | 0.64    | 0.57    | 0.533  | 0.757   | 0.745   | 1.36     |    |
| Urea N (mgm. %)                |         |         |         |         |         |         |         | 21.0    |        | 15      |         |          |    |
| Uric acid (mgm. %)             |         |         |         |         |         |         |         | 4.3     |        |         |         |          |    |
| Creatinine (mgm. %)            |         |         |         |         |         |         |         | 1.2     |        |         |         |          |    |
| Fasting blood sugar (mgm. %)   |         |         |         |         |         |         | 59.6    | 71      |        | 92.6    | 100.5   | 83       |    |
| CO <sub>2</sub> (vol. %)       | 60.3    | 66.3    | 53.0    | 74.5    | 48.0    | 57.8    | 53      |         |        |         | 60.5    | 59.5     |    |
| Cl. (mgm. %)                   | 376     | 345     | 358     | 334     | 343     | 357     | 349     |         |        |         | 366     | 348      |    |
| Ca. (mgm. %)                   |         | 9.2     | 8.5     |         |         | 9.3     |         |         |        |         | 10.2    |          |    |
| P. (mgm. %)                    | 2.9     | 3.8     | 4.6     | 3.5     | 3.4     | 5.8     | 5.6     |         |        |         | 4.7     | 5.1      |    |
| K. (mgm. %)                    |         |         |         |         |         |         |         |         |        |         |         | 17.5     |    |
| Total base (m.eq./l)           | 150.5   |         |         |         |         |         |         | 132     | 164    |         | 150     | 150      |    |
| Cholesterol (mgm. %)           | 218     | 128     | 180     | 181     | 305     | 202     | 232     | 223     |        | 118     | 239     | 179      |    |
| Free cholest. (mgm. %)         |         |         |         |         |         |         |         | 61      |        |         |         |          |    |
| Unbound chol. (mgm. %)         |         |         |         |         |         |         |         | 33      |        |         |         |          |    |
| % unbound chol. (% of total)   |         |         |         |         |         |         |         | 15%     |        |         |         |          |    |
| % Free chol. (% of total)      |         |         |         |         |         |         |         | 27%     |        |         |         |          |    |
| Phosphatase .....              |         |         |         |         |         |         |         |         |        |         |         |          |    |

for 1 to 2 years before cylindruria appeared. In cases of recovery, the albuminuria may persist for long periods, even years after the apparent disappearance of all the other symptoms of amyloidosis.

Cylindruria usually appears much later than albuminuria. The casts present may be of all types, e.g., hyaline, granular, cellular and waxy. In the same patient, there will be a marked variability in the number and type of casts. They are usually present in very small numbers, no more than three casts being seen in a low power field. Rarely are they present in excessive amounts; they are often absent.

White blood cells and red blood cells are frequently observed but are not numerous.

In fact one ordinarily sees very few of these cellular elements in a low power field. In one case the urine was loaded with leucocytes and erythrocytes, which continued to be present even after the patient was apparently clinically well of amyloid disease. In this case, extensive genito-urinary investigation and various renal functional and chemical examinations gave normal findings.

In the earlier stages of amyloidosis, all the 16 tested patients showed a normal urinary output and a normal ability to concentrate. In 6 of these cases, as the disease progressed

#### Secondary amyloidosis

| T. F. |         | E. Z.   |         |         |          |         |         | V. C.   |         |         | F. S.   |         |         |         |
|-------|---------|---------|---------|---------|----------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| 4     | 9/29/35 | 8/28/36 | 9/15/33 | 9/24/34 | 10/15/35 | 8/28/36 | 6/10/38 | 6/29/34 | 9/24/35 | 9/11/36 | 9/24/34 | 9/24/35 | 9/22/36 | 6/10/38 |
|       | ++      | 0       | ++++    | +++++   | +++      | ++      | +-      | +++     | +++++   | +++++   | +++     | ++      | +-      | 0       |
|       | 1230    | 1063    | 847     | 898     | 935      | 898     | 770     | 1370    | 1098    | 951     | 1255    | 1365    | 1352    | 1415    |
|       | 32      |         | 36      | 31      | 31       |         | 26.2    | 33      | 35      | 30      | 33      | 39      | 26      | 26.4    |
|       | 7.5     | 6.56    | 5.16    | 5.40    | 5.66     | 5.55    | 4.81    | 8.33    | 6.63    | 5.76    | 7.64    | 8.29    | 8.29    | 8.85    |
|       | 3.84    | 3.91    | 1.72    | 2.06    | 2.19     | 2.52    | 1.72    | 2.78    | 2.03    | 1.13    | 2.94    | 3.94    | 4.04    | 4.31    |
|       | 3.66    | 2.58    | 3.44    | 3.34    | 3.47     | 3.03    | 3.09    | 5.55    | 4.60    | 4.63    | 4.70    | 4.35    | 4.25    | 4.54    |
|       | 1.05    | 1.55    | 0.50    | 0.618   | 0.63     | 0.83    | 0.56    | 0.50    | 0.44    | 0.24    | 0.625   | 0.91    | 0.95    | 0.95    |
|       |         | 13.2    |         |         |          | 10.2    | 8.9     |         |         | 9.7     |         |         | 13      | 11.0    |
|       |         | 3.7     |         |         |          | 4.5     | 4.2     |         |         | 3.7     |         |         | 3.4     | 3.6     |
|       |         |         |         |         |          |         | 1.3     |         |         | 1.1     |         |         | 1.0     | 1.2     |
|       | 85      |         | 74      | 98      | 80       |         |         |         |         |         | 80      | 76      |         |         |
|       | 58      |         |         | 52.0    | 50.5     |         |         | 58.8    | 56.0    |         | 58.5    | 60      |         |         |
|       | 351     |         |         | 380     | 363      |         |         | 360     | 354     |         | 328     | 340     |         |         |
|       |         |         |         | 8.8     |          |         |         |         |         |         | 10.0    |         |         |         |
|       | 4.7     | 4.3     |         | 6.3     | 5.6      |         |         |         | 4.7     |         | 4.9     | 5.7     |         |         |
|       | 139     |         |         | 142     | 154      |         |         |         | 137     |         | 147     | 149     |         |         |
|       |         | 94      |         | 186     | 216      | 159     | 242     | 139     | 112     | 115     | 185     | 180     | 193     | 139     |
|       |         | 54      |         |         |          | 66      | 67      |         |         | 38      |         |         | 45      | 46      |
|       |         | 24      |         |         |          | 40      |         |         |         | 24      |         |         | 27      |         |
|       |         |         |         |         |          |         |         |         |         | 21%     |         |         | 19      |         |
|       | 57      |         |         |         |          | 41      | 28%     |         |         | 33%     |         |         | 23      | 33%     |
|       | 6.0     |         |         |         |          | 6.3     |         |         |         |         |         |         |         |         |
|       | units   |         |         |         |          | units   |         |         |         |         |         |         |         |         |

there occurred progressive diminution in quantitative excretion and concentration of the urine. As they reached the advanced lardaceous state the total daily excretion was under 1000 cc. and in most cases under 700 cc. The average was 400 to 500 cc. The specific gravity was low (under 1.010).

Anuria occurred in the terminal stages. It was preceded or accompanied by headache, vomiting, dyspnea, hiccup, and drowsiness. The drowsiness deepened until the patients became comatose. Death ensued within a few days after the onset of the coma. Rarely was this uremic syndrome accompanied by muscular twitchings or convulsions (2 cases).

*Blood Chemical Studies:* Blood chemical studies may reveal a changing picture depending

upon the nature and duration of the primary disease as well as upon the site of involvement and stage of development of the lardaceous state. With few exceptions, however, the blood protein findings follow a definite pattern which varies only quantitatively, depending upon the duration and severity of the disease (Table VIII). This general chemical alteration is, however, not peculiar to amyloidosis, but occurs frequently in a considerable number of different types of infections of several weeks duration or longer. The significance of these chemical findings in these diseases will be discussed in more detail in another communication (58). In the course of a persistent infection or chronic disease, even long before there is any presumptive evidence of amyloidosis, there usually occur certain changes in the blood proteins. At first the total serum protein may be normal or slightly increased; the serum globulin shows a perceptible increase and continues to increase slowly. Then the serum albumin decreases gradually so that eventually the albumin-globulin ratio decreases and becomes inverted. In the course of this process after an initial slight and brief rise, there is a progressive lowering in the total serum protein, due at first to the decrease of the serum albumin and later also to the decline of serum globulin. The total serum protein may be as low as 3 per cent (55, 59). In our series when presumptive evidence for the existence of amyloidosis was present, the total serum-protein was normal and usually in the lower range, with inversion of the albumin-globulin ratio. The same findings were usually present when the findings in favor of amyloidosis were more striking and more definite. A few of our cases with long-continued severe symptoms showed the more pronounced chemical changes. Any of the above protein blood changes may be present irrespective of the duration of amyloidosis; and in the same subject the total serum protein and its albumin and globulin fractions may display significant quantitative fluctuations on different occasions, although the inversion of the albumin-globulin ratio will persist.

Extensive amyloid deposition in the liver with considerable atrophy of liver cells may lead to impairment of hepatic function and characteristic blood changes. Similarly, if there is a great deal of diffuse structural change in the renal elements with functional disturbances, there may be corresponding chemical alterations in the blood. Since in most instances, except perhaps terminally, both hepatic and kidney functions are within normal limits, the range of blood non-protein nitrogen and blood urea nitrogen is usually normal. However, in very advanced cases or when marked renal impairment occurs, both the blood urea and non-protein nitrogen may increase (56). A rise of non-protein nitrogen to 100 mgm. per 100 cc. of blood shortly before death has been reported in two cases (54). An average increase of 49 to 60 mgm. per cent of blood urea nitrogen has been observed. In our group, only in 3 instances did the blood non-protein nitrogen rise to 40 mgm. per cent or above, with the average range between 30 to 35 mgm. per cent (Table VIII). No special blood urea nitrogen studies were made but it is very likely that with very marked functional hepatic derangement, there will be a tendency to a decrease of this proteolytic function. One case in which such investigation was made tends to support this view. In this case, with severe liver parenchymal atrophy, repeated determinations showed 4 to 6 mgm. of urea.

Most reports in which mention is made of blood sugar in cases of amyloidosis, give normal levels. However, in our small series of 14 cases, there was a tendency to low normal post-absorptive blood values, e.g., 60 to 80 mgm. per cent. In all these patients there was marked hepatic amyloidosis (Table VIII).

Because of our limited facilities for blood lipid studies, no very extensive investigation was attempted. The blood cholesterol and its fractions showed no significant changes at any stage of the disease, including instances when the so-called "nephrotic syndrome" appeared or when the liver was tremendously enlarged. The total blood cholesterol ranged from approximately 100 to 239 mgm. per cent (Table VIII). King and Bruger (60) observed a tendency to a sharp decrease in the blood cholesterol in cases terminating fatally within a relatively short time. They consider a low blood cholesterol of grave prognostic significance. We have been unable to confirm this conclusion.

The blood electrolytes such as blood bicarbonate, sodium, chloride, calcium and phosphorus remained constantly within normal limits in our series (Table VIII).



*Blood count:* Examination of the peripheral blood at the stage when classical symptoms of amyloidosis were evident, revealed varying degrees of hypochromic microcytic anemia. Of 35 cases, 11 showed a hemoglobin of 50 per cent or less; 21 of 60 per cent or less; and in the remaining 14 cases it ranged between 60 and 70 per cent. In the majority of instances, the total erythrocytes per cu. mm. were between 3 to 4 million although there were some in which there were over 4 million. There were only 9 cases in which the red blood cells were under 2 million per cu. mm. There is therefore a much sharper decrease in the hemoglobin resulting in a low color index. In most cases there was a slight to moderate leucocytosis, which was not greater than that seen in uncomplicated chronic infections. The proportion between the different types of leucocytes was generally within normal limits and apparently depended upon the nature and severity of the primary disease.

*Congo Red Test:* That the Congo red test is a valuable diagnostic measure no one denies (61-64). Some doubt has been expressed as to its specificity for the diagnosis of amyloidosis. Altnow et al (54) believe that there is such marked fluctuation in the response of subjects with amyloidosis to the dye that extreme caution in the interpretation of the results of this test is warranted. The presence of Congo red absorption of even 75 per cent of the injected dye has been reported in tuberculous cases without amyloid as proven by detailed autopsy examination (65). The test must therefore be considered as of little moment in the absence of symptoms or signs of amyloidosis.

Recently Harmon and Kernwein (66) suggested a quantitative technic for the Congo red test. They insisted upon 100 per cent retention as the only value on which a positive diagnosis of amyloidosis could be based; any lesser degree of retention could be regarded merely as presumptive evidence of the presence of amyloid. They further suggested that the regression of the disease was paralleled by lesser degrees of dye retention. This work has not yet been confirmed.

We employed the technique described by Bookman and Rosenthal (63). Eight to fifteen cu. cm. of a 1.2 per cent solution of Congo red, depending upon the age and size of the patient, were injected intravenously. The test is comparatively harmless although more than half of our subjects experienced a severe chill and elevation of temperature to 103°F. or 104°F. or over. The temperature rapidly subsided. In all our tested patients (59 untreated, 16 treated cases), there was 100 per cent retention of the dye at the end of one hour.

#### DIAGNOSIS

The diagnosis of secondary generalized amyloidosis depends upon a careful correlation and evaluation of the clinical symptoms and laboratory data, including the Congo red test. The diversity of organs involved in amyloidosis and the variability of the lesions in the affected organ does not warrant the consideration of any particular symptom or combination of symptoms as necessary for a diagnosis. Many cases would be undiagnosed if one always insisted on the triad of albuminuria, hepatomegaly and splenomegaly (54, 55, 59, 67). To entertain the diagnosis of amyloidosis, one should have the following: 1) the existence of a long continued infection and particularly one with suppuration; or the presence of one or the other of the known causes of lardaceous disease; 2) clinical signs indicating amyloid change in the liver, spleen or kidneys, or in two of these organs. A positive Congo red test supports the diagnosis. Although cases have been reported where amyloidosis appeared within 3 months after the onset of the primary illness, such instances are very rare and one may have to allow 6 to 12 months to elapse after the onset of the inciting disease before the diagnosis of amyloidosis may be made with certainty.

Amyloidosis of the liver may be differentiated from other hepatic enlargements by the existence of a cause for its development and the presence in almost

all cases of splenic and even renal involvement. Leukemia may be eliminated by a hematological study including, in doubtful cases, bone marrow puncture studies; fatty liver or a hydatid cyst of the liver or neoplasm of the liver by the presence of a causative factor, splenomegaly, albuminuria, cylindruria, blood protein changes and a positive Congo red test and, if necessary, by thorotrast visualization of the neoplasm or serologic or immunologic reactions for hydatid disease; cirrhosis of the liver by evidence of the primary disease, renal symptoms (if present) and the dye test. A negative Wassermann, Kahn or Kline test will usually rule out a luetic liver. On the other hand, if the serological reaction is positive, one must resort to the therapeutic test to determine if the hepatomegaly is due to a syphilitic liver or to amyloidosis caused by lues. The latter is improbable if there occurs a rapid diminution in the size of the organ with anti-syphilitic treatment.

Splenic enlargements must be differentiated in the same manner. Amyloidosis of the spleen is usually associated with hepatomegaly, and in many instances with renal amyloidosis. A careful history and examination will usually reveal an underlying primary causal disease. In doubtful cases splenic or hepatic puncture and biopsy study can be done with safety and ease (68).

Renal amyloidosis will vary in its clinical features depending upon secondary renal changes. There may be a syndrome which resembles chronic nephrosis or one stimulating chronic glomerulonephritis. However, there are certain findings characteristic of a relatively pure lardaceous condition of the kidneys which help to separate it from the other two types of nephritis, e.g., albuminuria, cylindruria, leucocytes and erythrocytes in the urine, normal eye grounds, hypotension or normal blood pressure, low serum protein with inversion of albumin-globulin ratio and normal blood cholesterol. In addition the non-protein nitrogen levels are usually normal except in the terminal stages. Then again its association with a basal disease responsible for amyloidosis, the cachexia, hepatomegaly and splenomegaly (if present) all substantiate the diagnosis.

#### COURSE

Individuals vary in their susceptibility to amyloidosis and in their clinical course, once the lardaceous process begins. The nature and severity of the initial condition, even though it is the causal agent, are not the sole determining factors as evidenced by the variability in the rate of development, degree and extent of involvement of amyloidosis in different individuals; and also by the absence of amyloidosis in other individuals even under apparently similar conditions (65). There are, apparently, several factors that play a determining rôle in the onset, severity and duration of amyloidosis.

The primary disease must persist for long periods of time, causing a more or less continuous marked metabolic disorder. If the initial condition is relapsing in nature, and its periods of activity of short duration alternating with periods of quiescence of long duration, amyloidosis will probably not develop or will progress slowly. On the other hand, if there are no remissions, or very short ones, the lardaceous changes will develop rapidly. One cannot however dis-

regard the effect of amyloidosis upon the initial disease which in turn exercises a mutually accelerating influence upon the lardaceous process (13).

That the reticulo-endothelial system plays an important rôle in the production and development of amyloidosis has been proved experimentally by several workers (8b, 16, 26, 27-29). From the very beginning of the disease process, the fixed and wandering macrophages of the reticulo-endothelial system show definite responses and changes which are progressive in character. The changes, in time, become marked and widespread leading to profound structural and functional alterations. The more advanced the lardaceous disease is, the more severe and extensive is the involvement of the reticulo-endothelial system. The inherent capacity of the reticulo-endothelial system to respond to the pathological condition varies with each individual. Consequently, different persons will react differently both in the rate and degree of development of amyloidosis.

Diet probably exercises an influence upon the production and course of amyloidosis (8, 9). A thoroughly adequate diet, rich in all food components, was found to retard the onset and progress of the lardaceous disease in white mice as compared with other diets ordinarily sufficient for life and growth. Vitamins A and B complex in combination appeared to exercise a similar retarding effect.

A factor present in liver exerts a favorable influence upon amyloidosis (7-11, 15). Its administration to human beings and to white mice will cause a distinct retardation of the disease; and if the disease is not too advanced, and the primary disease not too fulminating it will result in the resorption of the amyloid material. This will occur even in the presence of an active primary infection (9).

#### PROGNOSIS

Whenever the primary infection could not be terminated within a reasonable time (about 3 years or less), all cases in this series of moderately advanced to advanced amyloidosis died, unless they were treated with a liver preparation. Clinical experience has compelled physicians in the past to regard generalized secondary amyloidosis as an almost universally fatal disease. Ordinarily an individual with this disease continues to show an unfavorable progression of symptoms until finally death occurs from the primary illness, or an intercurrent infection, or from amyloidosis as a result of extensive involvement of an important organ such as the kidneys. Once unquestioned amyloidosis was present, recovery has been rare. This was due to the more or less constant effect of the causal disease which continued to be active and led to progression of the amyloidosis; and to the reciprocal influence of amyloidosis in aggravating and in causing the persistence of the primary illness. There have been occasional reports of recovery (7, 8, 10, 11, 14, 68-76). These followed, in most cases, surgical procedures which early terminated or arrested the primary disease; and in very exceptional instances after spontaneous cessation of the initial infection. That amyloid may be resorbed has received experimental confirmation (8, 9, 15, 68). With the introduction of liver therapy, the authors feel that a significant number of subjects with amyloidosis will be benefited and will recover after persistent

use of a potent preparation. In our series, all patients, e.g., 69, not treated with the liver product died within 2 years. On the other hand, of 16 cases receiving this therapy, 12 showed definite prolongation of life, or clinical improvement. Nine have been definitely cured with disappearance of all clinical symptoms and total absence of Congo red retention; and 2 have shown striking improvement in their condition up to the present time (Table VIII).

#### TREATMENT

Prophylactic measures must be employed to prevent the onset of amyloidosis. Causal diseases must be treated adequately to decrease their duration to a minimum and to prevent suppuration. The primary disease, particularly if it be tuberculous, should be recognized and treated early to prevent its progress to a malignant form. The more advanced forms should be subjected in a positive manner to various modern methods including surgery. In addition, hygienic and nutritional measures such as rest, fresh air, an adequate diet rich in all minerals and vitamins, sunlight and heliotherapy where indicated should be provided. If the serum protein is low and marked albuminuria is present, a high protein diet should be prescribed provided, of course, there is no significant impairment of renal function and retention in the nitrogenous products of the blood. To ameliorate distressing edema or anasarca that may be present due to lowered serum protein a blood or plasma transfusion may be tried. Diuretics have been found to be of little benefit. Abdominal paracentesis is contra-indicated. Fluid very quickly reaccumulates and its rate of accumulation increases rapidly with each successive tap. One only serves to deplete a patient of his valuable protein material and to hasten his demise. Liver therapy, however, has been found to lead to dramatic decrease or to disappearance of transudates in various parts of the body (9).

In addition to the treatment of the underlying cause for amyloidosis, the daily administration of a desiccated powdered whole liver preparation in doses of 4 to 8 gm., three times a day, is recommended. Our earlier experimental and clinical work (7-9) was done with a liver extract prepared by desiccation in vacuo at a temperature below 35°C. Subsequent to the publication of our clinical paper (9), the company making this preparation went out of business, and we have not yet found an oral commercial preparation experimentally potent. Lilly's and Biscoff's crude liver extracts for parenteral use have shown a fair degree of efficacy.

Since the treatment must be continued for a long period of time and parenteral extracts are generally very costly, we resorted to the following simple method of preparing orally effective liver (77).

Liver obtained fresh from an abattoir is cleansed of its gross extraneous matter, especially gross blood vessels. It is then cut into cubes and passed through a Sep-Ro Siv. The very fine sieve of the latter is used, the liver forced through the machine several times in order to reduce the product to a fine, pasty consistency.

Fruit juices are added to wash as much of the liver as possible through the sieve of the machine. The finely mashed liver will protrude through the pores

of the sieve, while any attached tough muscle, fibrous tissue, or large blood vessels will be extruded through the end of the funnel. This residue from the funnel should again be put through the machine several times, for it thereby helps clean the teeth of the grinder of considerable retained valuable liver mash. A spoon is finally used to free the sieve of adherent macerated liver.

The pressed tissue and the juice are collected in a bowl. Additional fruit juice is added to thin out the mixture, and this is then passed through a fine scoop sieve that can be purchased in any five-and-ten-cent or hardware store. The finished mash should be totally free from lumps of liver. It generally resembles a chocolate drink in color. The taste is that of the fruit juice used, is quite palatable, and is taken readily. A mixture of orange and pineapple juice is the vehicle most popular with our patients; any juice, however, may be used to suit the patient. The liver preparation should be kept in a cold refrigerator or icebox. In the event that the drink is too thick, additional fruit juice may be added to suit the patient's demand. At certain times of the year the liver may have a pungent taste. Washing one's mouth with unadulterated fruit juice, or chewing a few gum drops will easily and rapidly overcome this taste.

This procedure gives an approximate yield of 90 per cent. The dosage varies from the equivalent of  $\frac{1}{4}$  to  $\frac{3}{4}$  of a pound of liver daily. Wherever possible, the use of mash prepared daily is recommended. We have found, however, that a three day supply kept at a temperature of 8°F. or lower is equally potent and palatable. After four or five days the juice becomes mildly sour. Two pounds of liver and one quart of fruit juice yield a total of about two quarts of the final mash, a supply sufficient for three days. In a well established case of generalized amyloidosis, no other therapeutic measure has been of value in our series.

Several observers have reported failures with liver therapy. These results are at variance with our own. These failures have been reviewed in greater detail in another paper (9). It is important to note, however, that an analysis of these failures reveals the fact that various liver extracts were used without animal experimentation to determine their potency for amyloidosis, or that treatment was carried out for less than a year, a period insufficient, especially in moderately advanced cases, for permanent results. Such analysis further shows that liver therapy was discontinued, either by the disappearance of the patient or by election, at or about the time of apparent relapses of the amyloid disease.

Recently Harmon and Kernwein (78), reviewing our earlier work, suggested that only two of our six treated cases properly could be considered recovered, the other four being in the stage of spontaneous remission. They based this statement on the presence of appreciable absorption of Congo red and albuminuria in these cases at the time of total regression of all other signs and symptoms of the disease in our cases. We have never seen, in untreated cases, such marked recession of symptoms; and our earlier experimental work (7, 8) indicated that spontaneous disappearance of appreciable amounts of amyloid does not occur. Nevertheless, we re-examined our original records and found that all our treated cases initially had had 100 per cent dye retention. We then re-examined these



recovered cases. As of the date of submission of this paper (October 1944) of these cases, 9 (Cases 1, 2, 6-11, 15, Table VII) show no dye retention. Case 14 still shows 56 per cent retention, Case 16 shows 60 per cent retention. Albuminuria is still present in Cases 1, 7, 8, 11, 14-16.

Cohen (25) recently felt that liver therapy did not materially affect the outcome in his cases. In 30 cases, the basic oral therapy consisted of a high protein diet, iron, and dilute hydrochloric acid. Twenty-three patients also received parenteral therapy, chiefly liver extract, the dose averaging the equivalent of 51 grams of powdered whole liver per week. While exact comparisons are impossible, it is our opinion that this dose was utterly inadequate, since our experience has shown us that a minimum of 4 grams three times a day (84 grams per week) was needed to achieve satisfactory results, and that the results were better when doses in the neighborhood of 150 grams per week of powdered whole fresh liver were used. Even with the doses he employed, Cohen found definite objective improvement in 4 patients.

In treating chronic infections complicated by amyloidosis, one must realize the marked tendency to relapses in such conditions and even with liver therapy, such remission may occur. However, persistence in the administration of a potent liver product will in many cases reward the patient's physician and the afflicted subject.

#### SUMMARY

1. A clinical and pathological analysis of 84 cases of generalized amyloidosis secondary to tuberculosis has been presented.

2. The disease is more frequent in males and its incidence is highest in the early decades of life.

3. Amyloidosis occurs in most instances within 3 to 5 years after the onset of the primary infection.

4. Existence of sinuses tends markedly to accelerate the development of amyloidosis.

5. Symptomatology and clinical pathological findings and course and factors determining prognosis are described.

6. Practically all patients with moderately advanced amyloidosis died eventually if treated with the usual medical and surgical measures. The majority of cases died within 2 years of onset of amyloid disease.

7. The administration of a desiccated whole liver preparation in suitable doses and over an adequate period of time is an effective curative measure in a significant number of cases, even with advanced amyloidosis and even in the presence of continued activity of the primary infection.

#### BIBLIOGRAPHY

1. ROSENBLATT, M. B.: Amyloidosis and amyloid nephrosis. *Am. J. M. Sc.*, 186: 558, 1933.
2. ROSENBLATT, M. B.: Clinical manifestations of amyloidosis. *Ann. Int. Med.*, 8: 679, 1934.
3. FISHBERG, M.: *Pulmonary Tuberculosis*. Philadelphia, Lea & Febiger, ed. 4, p. 222, 1932.

4. Personal communication from Dr. Oscar Auerbach, pathologist, Sea View Hospital for Tuberculosis, New York City.
5. SALEEBY, E. R.: Question of the existence of amyloid casts. *J. A. M. A.*, 84: 344, 1925.
6. WALDENSTROM, H.: Om Amyloidens Uppkonist Och Forsrinnande hos Barn. *Nord. Med. Tidsskrift.*, 2: 353, 1930.
7. GRAYZEL, H. G., JACOBI, M., MASLOW, H., AND WARSHALL, H. B.: Experimental studies of amyloidosis. *Proc. Soc. Exper. Biol. & Med.*, 28: 172, 1930.
- 8a. GRAYZEL, H. G., JACOBI, M., WARSHALL, H. B., BOGIN, M., AND KRAMER, B.: Clinical and experimental studies in amyloidosis. *Acta Paediatrica*, 26: 177, 1933.
- b. GRAYZEL, H. G., JACOBI, M., WARSHALL, H. B., BOGIN, M., AND BOLKER, H.: Amyloidosis: Experimental studies. *Arch. Path.*, 17: 50, 1934.
9. GRAYZEL, H. G., AND JACOBI, M.: Secondary amyloidosis: Results of therapy with desiccated whole liver powder. *Ann. Int. Med.*, 12: 39, 1938.
10. WHITBECK, B. H.: Livermeal in the treatment of amyloidosis in surgical tuberculosis. *J. Bone & Joint Surg.*, 14: 85, 1932.
11. KENNEDY, W. R.: Renal amyloidosis. *Canad. M. A. J.*, 33: 385, 1935.
12. OPPENHEIMER, B. S., AND SILVER, S.: Recession of renal amyloidosis due to multiple skin gangrene associated with arteritis of the skin. *J. Mt. Sinai Hosp.*, 4: 851, 1938.
13. TRASOFF, A., SCHNEEBERG, N., AND SCARF, M.: Recovery from multiple rheumatoid arthritis complicated by amyloidosis in a child: Report of case and review of literature. *Arch. Int. Med.*, 74: 4, 1944.
14. ROSENBLATT, M. B.: Recovery from generalized amyloidosis secondary to pulmonary tuberculosis: Report of a case. *Arch. Int. Med.*, 57: 562, 1936.
15. CAVALUCCI, G.: Osservazioni sull' amiloidosi sperimentali. *Pathologica*, 26: 303, 1934.
16. JAFFE, R. H.: Amyloidosis produced by injections of proteins. *Arch. Path. & Lab. Med.*, 1: 26, 1926.
17. LETTERER, E.: Experimentelle Studien uber Art und Entstehung des Amyloids. *Zentralbl. f. inn. Med.*, 47: 417, 1926.
18. LETTERER, E.: Recent investigations concerning the development of amyloid. *Virchow's Arch. f. path. Anat.*, 293: 34, 1934.
19. LOESCHCKE, H.: Vorstellungen uber das Wesen von Hyalin und Amyloid auf grund von serologischen Versuchen. *Beitr. z. path. Anat. u. z. allg. Path.*, 77: 231, 1927.
20. LUCKE, B., AND MARKLEY, L. A.: Difference in susceptibility of mice and rats to experimental production of amyloidosis. *Proc. Soc. Exper. Biol. & Med.*, 25: 642, 1928.
21. KUCZYNSKI, M. H.: Edwin Goldmann's Untersuchungen uber cellulare Vorgange im Gefolge des Verdauungsprozesses auf Grund nachgelassener Präparate dargestellt und durch neue Versuche ergänzt. *Virchows Arch. f. path. Anat.*, 239: 184, 1922.
22. KUCZYNSKI, M. H.: Neue Beiträge zur Lehre vom Amyloid. *Klin. Wehnschr.*, 2: 727, 1923.
23. MAGNUS-LEVY, A.: Multiple Myelome: Eugglobulinämie. Zur Klinik und Pathologie. Amyloidose. *Ztschr. f. klin. Med.*, 126: 62, 1933.
24. EKLUND, C. M., AND REIMANN, H. A.: The etiology of amyloid disease. *Arch. Path.*, 21: 1, 1936.
25. COHEN, S.: Amyloidosis complicating tuberculosis—Diagnosis, prognosis, and treatment. *Ann. Int. Med.*, 19: 990, 1943.
26. SMETANA, H.: Relation of the reticulo-endothelial system to the formation of amyloid. *J. Exper. Med.*, 45: 619, 1927.
27. ARNDT, H. J.: Retikuloendothel und Amyloid. *Verhandl. d. deutsch. path. Gesellsch.*, 26: 243, 1931.
28. DOERKEN, E.: Histologische Untersuchungen bei Serumpferden mit besonderer Berücksichtigung des Amyloidablagerungen. *Virchows Arch. f. path. Anat.*, 286: 487, 1932.

29. STOEGER, E.: Betrachtungen über sog. genuine Amyloidose. *Deutsch. Arch. f. klin. Med.*, 176: 642, 1934.
30. HAAS, G.: Studies of amyloid. II. The isolation of a polysaccharide from amyloid-bearing tissues. *Arch. Path.*, 34: 92, 1942.
31. ODDI, R.: Ueber das Vorkommen von Chondroitinschwefelsäure in der Amyloidleber. *Arch. f. exper. Path. u. Pharmacol.*, 33: 376, 1894.
32. KRAKOW, N. P.: Vorträge zur Chemie der Amyloidentartung. *Arch. f. exper. Path. u. Pharmacol.*, 40: 195, 1898.
33. HANSEN, O.: Ein Beitrag zur Chemie des Amyloiden Entartung. *Biochem. Ztschr.*, 13: 185, 1908.
34. EPPINGER, H.: Zur Chemie der Amyloidentartung. *Biochem. Ztschr.*, 127: 107, 1922.
35. THANNHAUSER, S. J., AND MAGENDANTZ, H.: The different clinical groups of xanthomatous diseases. *Ann. Int. Med.*, 11: 1662, 1938.
36. MOSCHCOWITZ, E.: Clinical aspects of amyloidosis. *Ann. Int. Med.*, 10: 73, 1936.
37. GERBER, I. E.: Amyloidosis of bone marrow. *Arch. Path.*, 17: 620, 1934.
38. BIRCH-HIRSCHFELD, F. V.: *Lehrbuch d. path. Anat.*, ed. 2, Leipzig, F. C. W. Vogel, 1882, vol. 1, p. 45.
40. CHARRIN, A.: La maladie pyocyane. Reviewed in *Arch. de Medecine Experimentale et d'Anatomie Pathologique*. 1<sup>re</sup> serie. Tome premier, p. 753, 1889.
41. RAUBITSCHKE, H.: Zur Kenntniss des Amyloids. *Verhandl. d. deutsch. path. Gesellschaft, Vierzehnte Tagung*, p. 273, 1910.
42. DANTSCHKOW, V.: Über die Entwicklung und Resorption experimentell erzeugter Amyloidsubstanz in den Speicheldrüsen von Kaninchen. *Virchows Arch. f. path. Anat.*, 187: 1, 1907.
43. DAVIDSON, C.: a. Ueber experimentelle Erzeugung von Amyloid. *Virchows Arch. f. path. Anat.*, 150: 16, 1897; b. Zur Erkennung zweier Stadien der Amyloidkrankung. *Ibid.*, 155: 382, 1899; c. Untersuchungen über die Ätiologie des Amyloids. *Ibid.*, 192: 226, 1908.
44. NOWAK, J.: Experimentelle Untersuchungen über die Ätiologie der Amyloidose. *Virchows Arch. f. path. Anat.*, 152: 162, 1898.
45. BENNHOLD, H.: Eine spezifische Amyloidfärbung mit Kongorot. *München. med. Wchnschr.*, 69: 1537, 1922.
46. SMETANA, H.: Experimental study of amyloid formation. *Bull. Johns Hopkins Hosp.*, 37: 383, 1925.
47. RIBBERT, O.: *Lehrbuch der allg. Path. u. d. patholog. Anatomie*. Leipzig, F. C. W. Vogel, 1923, pp. 96 et seq.
48. ASCHOFF, L.: Reticulo-Endothelial System, in *Lectures on Pathology*. New York, Paul B. Hoeber, Inc., 1924, p. 1 et seq.
49. Quoted from RIBBERT (ref. 47), AND KAUFMANN, E.: *Spezielle Pathologische Anatomie*, ed. 8, Berlin, Walter De Gruyter & Co., 1922, pp. 79, 184, 248, 439, 635, 742, 743, 954, 1066, 1128.
50. FERRARO, A., AND DAMON, L. A.: Histogenesis of amyloid bodies in central nervous system. *Arch. Path.*, 12: 229, 1931.
51. Tuberculosis Institutions in J. A. M. A., 105: 1865, 1935.
52. PEARLMAN, A. W.: Amyloidosis: Clinical and pathological study of 135 cases. *Quart. Bull. Sea View Hosp.*, 6: 295, 1941.
53. BRONFIN, I. D., AND GUTTMAN, P. H.: Amyloid degeneration of the adrenals as a factor in producing symptoms of Addison's Disease in chronic tuberculosis. *Am. Rev. Tuberc.*, 31: 1, 1935.
54. ALTNOW, H. O., VAN WINKLE, C. C., MALT, H. W., AND WILLIAMS, L. E.: Renal amyloidosis. *Arch. Int. Med.*, 56: 944, 1935.
55. BANNICK, E. G., BERKMAN, J. M., AND BEAVER, D. C.: Diffuse amyloidosis. *Arch. Int. Med.*, 51: 978, 1933.

56. DIXON, H. M.: Renal amyloidosis in relation to renal insufficiency. *Am. J. M. Sc.*, 187: 401, 1934.
57. BAUER, R.: Zur Frage der Nephrose, speziell der Syphilisnephrose. *Med. Klin.* 27: 1412, 1931.
58. GRAYZEL, H. G., JACOBI, M., AND MILLER, P.: To be published.
59. HAWKES, R. S.: Chronic arthritis with recent edema of feet. *New England M. J.*, 208: 757, 1933.
60. KING, S. E., AND BRUGER, M.: Plasma cholesterol in tuberculosis and amyloid disease. *Ann. Int. Med.*, 8: 1427, 1935.
61. BENNHOLD, H.: Excretion of intravenously injected Congo red in different diseases, especially amyloidosis. *Deutsch. Arch. f. klin. Med.*, 143: 32, 1923.
62. SCHONBERGER, E., AND ROSENBLATT, J.: Bennhold's intravenous injection of Congo red. *Wien. Klin. Wehnschr.*, 38: 113, 1925.
63. BOOKMAN, A., AND ROSENTHAL, J.: The clinical value of intravenous injection of Congo red in diagnosis of amyloid disease. *Am. J. M. Sc.*, 173: 396, 1927.
64. WALLACE, J.: Diagnosis of amyloid disease by intravenous injection of Congo red. *Lancet*, 1: 391, 1932.
65. LIPSTEIN, S., AND AUERBACH, O.: Congo red test. *Quart. Bull. Sea View Hosp.*, 2: 120, 1937.
66. HARMON, P. H., AND KERNWEIN, G.: Congo red test for amyloid disease. *Arch. Int. Med.*, 70: 416, 1942.
67. CHRISTIAN, H. A., in discussion of DUD, G. F., AND LEITER, L.: Experimental chronic diffuse amyloid glomerulonephrosis in rabbits produced by haemolytic Streptococci. *Tr. A. Am. Physicians*, 50: 138, 1935.
68. WALDENSTROM, H.: On the formation and disappearance of amyloid in man. *Acta chir. Scandinav.*, 63: 479, 1928.
69. KRETZSCHMAR, P. H., AND WESTBROOK, B. F.: A case of chronic empyema with extensive amyloid degeneration—Recovery. *Proc. Med. Soc. County Kings*, 5: 343, 1880.
70. OWENS, I.: Recovery from advanced lardaceous disease. *Proc. Med. Soc. London*, 9: 18, 1886.
71. GAIRDNER, W. P., in discussion of DELAFIELD, F.: On the disease of the kidneys popularly called Bright's disease. *Tr. A. Am. Physicians*, 6: 149, 1891.
72. HERRINGHAM, W. P.: *Kidney Diseases*. London, Oxford Univ. Press, 1912, p. 353.
73. NATHAN, M.: Ueber die klinische Diagnose der Amyloids mittels Kongorot-injektionen. *München med. Wehnschr.*, 75: 1883, 1928.
74. WALKER, G. F.: A case of recovery from amyloid disease. *Lancet*, 2: 120, 1928.
75. HABEIN, H. C.: Amyloidosis: Report of a case in which the patient recovered. *Proc. Staff Meet., Mayo Clinic*, 9: 261, 1934.
76. REIMANN, H. A.: Case of amyloidosis with recovery. *J. A. M. A.*, 104: 1070, 1935.
77. LOUKIDES, J., GRAYZEL, H. G., AND JACOBI, M.: A simple liver preparation orally effective in the treatment of human amyloid disease. *J. Lab. & Clin. Med.*, 28: 1321, 1943.
78. HARMON, P. H., AND KERNWEIN, G.: Utility of the Congo red test in diagnosis and differential diagnosis. *Arch. Int. Med.*, 70: 421, 1942.

## FIBROUS DYSPLASIA OF BONE

### A DISEASE ENTITY AND SPECIFICALLY NOT AN EXPRESSION OF NEUROFIBROMATOSIS

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In 1937, Albright and associates (1) reported on 5 cases of a "syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation, and endocrine dysfunction, with precocious puberty in females." Also in 1937, a study of a case representing the same condition was published by McCune and Bruch (2) under the title of: "Osteodystrophia fibrosa: Report of a Case in which the Condition was combined with Precocious Puberty, Pathologic Pigmentation of the Skin, and Hyperthyroidism." Both of these sets of authors also refer to a number of cases strikingly similar to theirs which had previously been reported in the literature under various titles.

In 1938, Lichtenstein (3), emphasizing particularly the pathology of the skeletal changes, described, under the name of "polyostotic fibrous dysplasia," 8 cases in which the skeletal lesions, though on the whole less widespread, were of the same type as in the cases reported by Albright and associates and McCune and Bruch but in which the manifestations of disease seemed to be limited to the skeleton. The description supplied in his paper of the pathologic alterations in the bones seemed to permit a sounder interpretation than had hitherto been given of the roentgenographic findings in the disorder, and in general to establish firmly the character of the skeletal changes constituting the nucleus of the disease. In 1942, Lichtenstein and Jaffe (4), on the basis of an enlarged experience then already covering 23 cases, expanded the conception of the disorder in question in a paper entitled "Fibrous Dysplasia of Bone: A Condition Affecting One, Several, or Many Bones, the Graver Cases of which may present Abnormal Pigmentation of Skin, Premature Sexual Development, Hyperthyroidism, or still other Extra-Skeletal Abnormalities."

On the basis of that expanded conception, cases such as were reported by McCune and Bruch, and Albright and associates (cases which were coming to be denoted in the literature as instances of Albright's disease) fell into place as representing the most florid expressions of the disorder as a whole. Specifically, it was pointed out that skeletal lesions constituted the common factor of the disease, and that, however variable their extent and severity, they appeared to be basically analogous in all cases. This conception was supported by analysis of the incidence of the extra-skeletal abnormalities occurring in the disorder. Indeed, it was found that these abnormalities (usually seen in combination) manifest themselves primarily in the cases in which the skeletal involvement is relatively severe and extensive. On the other hand, in the cases in which the skeletal involvement is milder or definitely mild, extra-skeletal abnormalities



may be few, and indeed the only one present may be one or more patches or some small spots of hyperpigmentation of the skin.

This interpretation, centering the disorder as a whole about the skeletal involvement, has been accepted by a number of other workers also, as indicated by the titles of pertinent papers accumulating in the literature. Falconer and Cope (5) entitle their contribution to the subject "Fibrous Dysplasia of Bone with Endocrine Disorders and Cutaneous Pigmentation (Albright's Disease)." In an addendum to their article they state that they too believe that what has come to be called Albright's disease is merely the severe form of "fibrous dysplasia of bone" in the wider sense of the term as used by Lichtenstein and Jaffe.

In 1944, Thannhauser (6), partly on the basis of some personal experience but mainly on the basis of a survey of the literature, attempted to give a new slant to the problem of the disorder. Specifically, he tries to establish the thesis that fibrous dysplasia of bone (or, as he prefers to call it, *osteitis fibrosa cystica localisata et disseminata*) is not an independent entity but is to be related by its clinical and histological features to neurofibromatosis of Recklinghausen. In support of this idea, he expresses the belief that the presence of hyperpigmented skin areas (*café au lait* spots and brown patches or blotches) in both *osteitis fibrosa cystica localisata et disseminata* and neurofibromatosis is in itself strong evidence linking the two conditions, since he regards such pigmentation as the basic expression of neurofibromatosis even without the presence of neurofibromatous nodules. In further support of the general thesis, it is stated that in the two conditions the bones show analogous fibromatous lesions, and that in both conditions these lesions are of neurofibromatous nature, though histologically they do not show nerve elements but rather only "whorls" of spindle cells. Indeed, it is maintained that a fibrous lesion showing whorls of spindle cells clearly betrays its neurofibromatous genesis through this whorled arrangement, for it is stated that in the center of such whorled lesions "a nerve fiber with schwannoglia was once present and initiated the fibrous growth." Finally, the occurrence of endocrine abnormalities (especially *pubertas praecox*) in association with both *osteitis fibrosa cystica localisata et disseminata* and neurofibromatosis is represented as offering additional corroboration of the interrelation of the two conditions.

The purpose of the present communication is to show that Thannhauser's thesis remains a hypothesis. Also, we shall try to show that it is a hypothesis not sustained by the findings in the cases from his own experience. Nor is it supported by those which he cites from the literature, which the present writer has himself surveyed in detail. Furthermore, the writer will undertake to show, on the basis of his own experience with both fibrous dysplasia and neurofibromatosis, that while the two conditions do overlap in respect to certain manifestations, there is ample clinical and anatomic evidence favoring a clear-cut distinction between the two.

*Skeletal Lesions of Fibrous Dysplasia.*—As already indicated, in any particular case of fibrous dysplasia, (our experience with which now covers about 30 cases) one, several, or many bones may be affected. When more than one

bone is affected, the involvement is often strictly unilateral and indeed not infrequently limited to several bones of one limb bud. Even when the skeletal involvement is extensive and bilateral, more bones are likely to be found affected on one side of the body than on the other. If the skull is also affected, its involvement, too, may be limited to one side, and if both sides of the body are affected the skull involvement is likely to be more severe on the side which is more severely affected as a whole.

Especially in cases showing multiple involvement, the area implicated in an affected bone is likely to be extensive. For instance, so far as the long bones are concerned, a substantial part of a shaft or all of it may be involved. Though the disease tends to spare the epiphysial ends of such bones, one or both of these too may be affected, but the contour of the articular surfaces seems usually to remain normal. Even in the cases in which only one bone is affected, a substantial part of it too is usually found involved, and the lesion is rarely very small in proportion to the bone as a whole (fig. 1A, B, and C).

Furthermore, however variable the extent and severity of the skeletal involvement in the various cases, the roentgenographic appearance and pathology of the lesions is basically the same in all. In the area involved, the interior of the bone is usually found to be filled by a rather rubbery and compressible tissue which may be more or less uniformly whitish or may show reddish speckling where there is vascular dilatation and congestion, and perhaps capillary hemorrhage. Fundamentally, this tissue is fibrous connective tissue. It may be gritty throughout from the presence everywhere in it of newly formed trabeculae of immature bone. On the other hand, it may show smaller or larger non-gritty highly collagenous areas in which few if any bony trabeculae are to be found. In some lesions, islands of hyaline cartilage may also be present within the fibrous connective tissue. Furthermore, in an occasional lesion, focal degeneration of this connective tissue may have led to the formation of one or more small secondary cysts. Occasionally, also, in some areas, so much bone may form in the connective-tissue substratum that the latter here sinks into the background (figs. 2A, B, and C).

All in all, the skeletal lesions in fibrous dysplasia develop in the interior of the affected bones or bone areas. While the contour of an affected bone as a whole may be found normal, it is often found distended in all or at least part of the affected area. The distension is the result of erosion of the cortex of the bone from the inside, consequent weakening of it, and yielding to the growing fibro-osseous tissue in the interior.

If the neck of the femur is involved, weakening of the bone may be associated with the development of a coxa vara or valga. Involvement of vertebral bodies may be associated with kyphosis or even kyphoscoliosis. A fracture may appear through a weakened and diseased area. Whatever malalignments, curvatures, fractures, or deformities of bones or bone areas one may see in association with fibrous dysplasia carry their explanation with them in that they occur in skeletal areas already modified by the presence, in the interior of the bone, of pathologic tissue of the kind we have described.

*Skeletal Lesions of Neurofibromatosis.*—Now let us juxtapose the skeletal involvement of fibrous dysplasia against that observed in association with neurofibromatosis. In the first place, it is clear that the skeleton is not involved

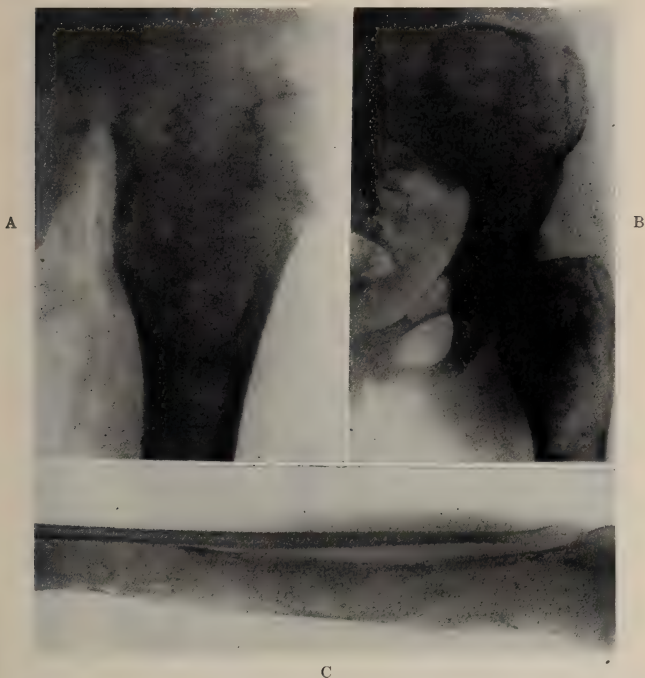


FIG. 1. A, Roentgenogram of a focus of fibrous dysplasia in the neck and adjacent portion of the shaft of a femur from a girl of 12. This was the only lesion present in this case.

B, Roentgenogram from a case of fibrous dysplasia in a girl of 20, showing involvement of the left innominate bone and the upper part of the femur. The rest of the femur was also affected, as was the tibia on the same side.

C, Roentgenogram from a case of fibrous dysplasia in a girl of 22, showing involvement of the right tibia. In this case, there was also involvement of the skull, the right femur, the pubis and ischium on both sides, the body of the 8th dorsal vertebra, and the 7th and 8th ribs.

in all cases of neurofibromatosis, though certainly in many. (The actual proportion of cases in which at least some skeletal aberration is present cannot be given, since in most institutions the skeleton is not routinely x-rayed in cases of neurofibromatosis.) Furthermore, the anatomic character of the skeletal involve-

ment in neurofibromatosis is by no means uniform from case to case, and in a case in which the skeletal involvement is pronounced, the abnormalities encountered may be of various types (7). In this respect, too, neurofibromatosis

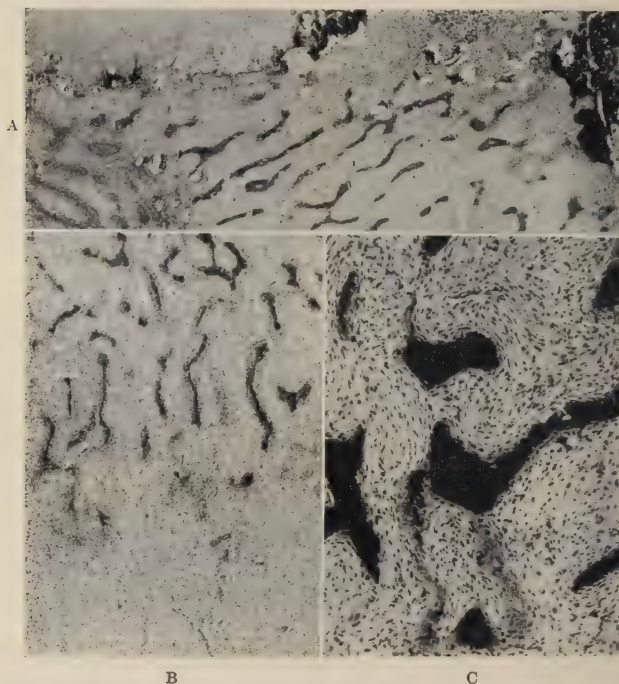


FIG. 2. A, Photomicrograph ( $\times 15$ ) showing the histologic structure of some tissue obtained by curettement of the femoral lesion in the case of fibrous dysplasia pictured in fig. 1B. a) cartilage, b) connective-tissue stroma undergoing osseous metaplasia, c) area of hemorrhage containing giant cells.

B, Photomicrograph ( $\times 15$ ) from the same lesion, showing another tissue area, in which, in one place, the stromal connective tissue has undergone osseous metaplasia while in another place it has not yet done so.

C, Photomicrograph ( $\times 45$ ) showing, in fuller detail, osseous metaplasia of the stromal connective tissue. (The tissue was not decalcified.)

contrasts strongly with fibrous dysplasia, in which the skeletal involvement follows a remarkably consistent anatomic pattern, whether one, several, or many bones are implicated in any given case. Finally, as will also be evident from what follows, the skeletal alterations in neurofibromatosis are not associated with the



presence, in the affected bones or bone areas, of pathologic tissue having the character of that consistently encountered in affected bones in cases of fibrous dysplasia.

The skeletal abnormalities preponderantly encountered in cases of neurofibromatosis are those which can be classed as anomalies of skeletal development or growth. As such, they reflect the fact that neurofibromatosis in general is a disease deeply rooted in the germ plasm. The congenital skeletal anomalies and developmental defects observed include: general gracility of the skeleton or of individual bones, localized abnormality of the gross internal architecture of a bone part, malformations of bone contours, abnormal length or abnormal shortness of bones (especially long bones), absence (complete or partial) of limb bones, pseudoarthroses, spina bifida, fusion of vertebral bodies, luxation of the hip, club foot, etc. (fig. 3A, B, and C).

Special interest attaches to the commonly observed distortions of the thoracic cage, centering principally around curvature of the vertebral column (fig. 4). This curvature frequently involves rotational torsion of part of the column, associated with sharp angulation and resulting in a pronounced kyphoscoliosis. The x-ray picture usually reveals wedging of several adjacent vertebral bodies in the angulated area, but on account of the distortion and the resultant overlapping shadows it is likely to be difficult to form a decisive opinion as to the nature of the underlying alterations. Indeed, we have but little information on the pathologico-anatomic basis of the kyphoscoliosis in these cases. That is, we do not know the relative importance in it of such factors as congenital defects of development of the vertebral bodies, or weakness and collapse of one or more bodies from the presence of neurofibromata in them (see below).

Gould (8) ascribed the pronounced kyphosis in the case (case 1) to which he largely devotes his article, to osteomalacic softening, and the findings in this case are widely invoked to explain kyphoscoliosis in neurofibromatosis in general as having an osteomalacic basis. Also pertinent to the larger question of the present paper is Gould's specific statement that in this case there was no sign of "ostitis fibrosa" anywhere in the skeleton. Be that as it may, there is need for further anatomic study of the deformed vertebral column that one encounters so often in cases of neurofibromatosis.

Finally, one encounters, though only occasionally, in a case of neurofibromatosis, one or more skeletal lesions due to the actual presence of a neurofibroma on a bone or within its interior. Specifically, a neurofibroma adjacent to a bone may, through direct pressure, cause an erosion defect on the surface of the bone. This has been described notably in relation to the calvarium. A neurofibroma developing in the periosteum may also erode the underlying cortex and give rise to a small blister- or bubble-like lesion between an eroded cortex and an elevated periosteum whose inner surface may be delimited by a shell of bone. Such bubble- or cyst-like lesions are rather small—usually not more than a centimeter in diameter—and do not resemble, either in location or general appearance, the lesions of fibrous dysplasia of bone. Brooks and Lehmann (9) illustrate one such small subperiosteal bubble-like lesion roentgenographically.



Furthermore, the only tissue specimen discussed by them in their article comes from a lesion which seems to be of this type, and specifically from a more or less globular extra-osseous, apparently subperiosteal tumor mass on the proximal



FIG. 3. A, Roentgenogram of the lower end of the right femur of a girl of 18 affected with neurofibromatosis. There was abnormal skin pigmentation, and numerous neurofibromata, some of which were proved by a biopsy, were present subcutaneously and along the course of several nerves. Note the abnormal shadow resulting from maldevelopment of the bone part.

B, Roentgenogram of the lower part of the left leg in this case, showing the absence (congenital) of a considerable part of the fibula. The companion tibia was 2 inches shorter than the one on the other side. Many other bones and bone parts also showed, in the x-ray films, deviations from the normal gross architectural structure.

C, Roentgenogram of right calcaneus, from same case, again showing a maldevelopment.

D, Roentgenogram showing a rarefied, expanded lesion in the left upper portion of the sacrum from a boy of 9 affected with neurofibromatosis. Abnormal skin pigmentation and numerous intracutaneous and subcutaneous fibromata, one of which was biopsied, were present. The child was admitted on account of severe sciatic pain, and presented, over the left sacroiliac region, a soft tender tumor mass 3 inches in diameter, the skin over which was red and beginning to ulcerate. This soft-tissue tumor seemed to be related to the lesion in the sacrum and was now suggestive of a sarcoma, although 3 years previously a biopsy had revealed a neurofibroma which was presumably benign.

end of a tibia. The excised lesion was found, on histologic examination, to be a neurofibroma delimited by a paper-thin shell of bone, presumably formed by the periosteum.



FIG. 4. Roentgenogram illustrating a sharp angular scoliosis presumably on the basis of a congenital anomaly, in a case of neurofibromatosis. The patient was a man of 22 who had had abnormal skin pigmentation and some scattered subcutaneous neurofibromata since early childhood. The scoliosis was definitely known to be present since the age of 14. One of the subcutaneous tumors was biopsied and proved to be a neurofibroma extending nearly to the epidermis, which showed melanin pigmentation of the basal cells. The insert (below) shows the curvature of the spine, the café au lait spots on the back, and some larger pigment blotches.

It is only the very occasional neurofibroma within the interior of a bone that offers even clinically any reasonable possibility of confusion with lesions of fibrous dysplasia (fig. 3D). The neurofibroma may have reached the interior

from the periosteum or developed *de novo* in the interior. In the report by Uhlmann and Grossman (10), case 1 seems to belong to the latter group. The patient in that case was a girl of 16 who presented what is described as a loculated cystic lesion in the right mandible. The photomicrograph of the biopsy specimen may very well represent a neurofibroma, though no gross or histologic description of the biopsy specimen is given in their paper. At any rate, it is clear from the illustration that, within the field shown, trabeculae of new bone are not a component of the histologic picture. Altogether, on the basis of that picture and the case as a whole, this mandibular lesion cannot be considered as analogous with a fibrous dysplasia lesion.

It may be well to review at this point the two personal cases cited by Thannhauser as "cases illustrating neurofibromatosis, *café au lait* spots and small fibrocystic bone lesions". In regard to the bone lesions of his case 1, it is observed that in the x-ray film "the lower end of the left femur showed an oval-shaped area of increased radiance, the size of a half dollar, cyst-like in appearance. The upper end of the right fibula also had an area the size of a dime of increased radiance". The final diagnosis of the bone lesions in this case is given as "bone cysts in the femur and fibula." In regard to case 2, it is stated that "x-ray examination showed an oblong rarefied area in the lower end of the left tibia," and the conclusion is drawn that this lesion was a "bone cyst in the tibia."

Thus the long-bone lesions in both these cases, as seen in the x-ray films, are designated as "bone cysts". The discussion of them, however, as noted further above, was started with the statement that they were "fibrocystic bone lesions." Furthermore, it is implied that these lesions are "osseous fibromata . . . located in the trabecular spaces of the long bones," of the nature of neurofibromata. On the basis of the scanty description of the roentgenographic appearance of the lesions in these two cases, the present writer does not venture to decide what these "cystic lesions" actually were. They may, indeed, have been intra-osseous neurofibromata, but such a definitive statement concerning the nature of a circumscribed rarefaction shadow in a long bone is certainly not justified in the absence of tissue examination, as our experience has repeatedly shown (11, 12), and there was no such examination in either of the two cases in question.

Furthermore, Thannhauser quotes cases 2, 3, 4, 23 and 27 in Stalman's paper (13) as showing the presence of "osteitis fibrosa cystica" lesions in the bones in cases of neurofibromatosis. However, when one turns to that paper, and surveys in turn the case histories and findings in each of these 5 supposedly pertinent cases, one fails to find that any anatomic proof is given which would sustain the claim that the bone lesions in these cases had an osteitis fibrosa basis. In only one of these cases (case 2) was a tissue examination ever done, and in that case the operative intervention (on a deformed femur) was done at another institution than Stalman's and the latter merely stated that the lesion was "allegedly [angeblich] *ostitis fibrosa*."

We come now to Thannhauser's contention that the lesions of fibrous dysplasia of bone are to be considered of neurofibromatous nature because they

show, in some places, whorls of spindle cells. Aside from the non-specificity, in general of the whorling of connective tissue fibers in a lesion, this generalization neglects in the first place the fact that the basic tissue of the bone lesions of fibrous dysplasia is a connective tissue possessing in high degree the capacity of undergoing osseous metaplasia. It not only can, but regularly does, undergo such metaplasia, often throughout the lesion, an intermingling of fiber bone and connective tissue being in fact the hall mark of the histologic picture of fibrous dysplasia of bone. Furthermore, the basic connective tissue undergoes not only osseous metaplasia, but in some lesions even cartilaginous metaplasia in some places. Thus the stromal tissue of fibrous dysplasia lesions, in contrast to that of neurofibromata, is essentially a connective tissue of osteogenic potentialities (figs. 2A, B and C). On the other hand, it is generally known that osseous and cartilaginous metaplasia is not inherent in the stromal tissue of lesions of neurofibromatosis, whether the lesions are located in the skin and subcutaneous tissues, in peripheral or central nerves, or on or within bones.

Furthermore, these lesions of neurofibromatosis, as a class, have also a histologic distinctiveness about them. This distinctiveness is derived from the presence, within their tangled basic stromal tissue, of degenerating nerve fibers, and, especially when the nerve fibers are few, of histologic formations of the nature of Schwannian hypertrophies (14, 15). In this connection, one does not have to enter the time-old controversy as to whether the basic stromal cells of the neurofibromas are of mesodermal nature and specifically fibroblasts derived from the endoperineural sheaths, or of neuroectodermal nature and derived from the cells of Schwann. Certainly no one who has studied the lesions of fibrous dysplasia of bone in detail has noted degenerating nerve fibers and tangles of stromal cells such as are characteristic of the architecture of neurofibromata, or areas containing the eddies of cells and palisades of nuclei that one sometimes sees in addition in neurofibromata.

#### SKIN PIGMENTATION IN FIBROUS DYSPLASIA VS. NEUROFIBROMATOSIS

Thannhauser holds that abnormal skin pigmentation, and not the presence of neurofibromata, is the *sine qua non* of neurofibromatosis. As already noted, the abnormal skin pigmentation in fibrous dysplasia is also used to identify that disorder with neurofibromatosis, the pigmentation in the two disorders being regarded as akin in every way. Thus, by playing up the abnormal skin pigmentation in both disorders, and playing down the actual neurofibromata (wherever located) in neurofibromatosis and the distinctive fibro-osseous character of the skeletal lesions in fibrous dysplasia, the two diseases are made practically interchangeable.

Nowhere in the literature quoted by Thannhauser in relation to the abnormal skin pigmentation in neurofibromatosis has the present writer found so exaggerated an emphasis on such pigmentation (admittedly very common and important) in the evaluation and diagnosis of that disease. It is true that the pigmentation has often been observed to precede the neural and skeletal manifestations of neurofibromatosis, and that it has sometimes been the most

conspicuous manifestation for a long time. Even in Parkes-Weber's case (16), however, a cutaneous neurofibroma was already present in association with the pigmentation when the patient first came to his attention, and several additional neurofibromata had developed in the skin when the patient was presented again three years later.\* The pigmentation is thus often a cue to the diagnosis of the disorder. However, the literature on the latter does not show that the presence of café au lait spots and brown blotches on the skin, by themselves and unassociated with other acknowledged manifestations of the disorder, represent neurofibromatosis unequivocally.

One does find incomplete forms (*formes frustes*) of the disorder in which the foreground of the total disease picture is occupied by one of the main facets of the disease complex: abnormal skin pigmentation, cutaneous neurofibromata, neurofibromata involving nerve trunks, or skeletal changes. However, in most if not all of these cases, the diagnosis of neurofibromatosis is supported by the presence of at least one or another of the other main manifestations. Thus Grenet and associates (17) have described, as representing a common "*forme fruste*" of the disease, cases in which the manifestations seemed to be limited, at least for a long time, to abnormal cutaneous pigmentation and skeletal involvement (particularly scoliosis or kyphoscoliosis) and in which the latter occupied the foreground of the clinical picture. In their opinion, even the idea that this cutaneo-osseous syndrome may represent neurofibromatosis required defense, but they felt it to be supported by the fact that among the antecedents and siblings of the subjects presenting this syndrome one can usually find complete and typical cases of the disorder.

In this connection, it is certainly also significant that no one has noted, among the antecedents and siblings of patients with fibrous dysplasia, any special prevalence of typical neurofibromatosis. Such a prevalence would have helped to interrelate the two disorders on a genetic basis. Actually, it is only neurofibromatosis that has a hereditary and familial basis at all, and that disease tends to be transmitted as such, while experience with fibrous dysplasia has not revealed any hereditary and familial tendency.

The attempt to approximate neurofibromatosis and fibrous dysplasia on the basis of the abnormal skin pigmentation is further weakened by other facts. It must be borne in mind that pronounced skin pigmentation is not at all regularly observed in cases of fibrous dysplasia. It is true that in the severer cases—especially the cases showing *pubertas praecox*—abnormal skin pigmentation is almost regularly prominent in the form of large brown patches or blotches associated with freckle-like or even larger spots. However, in the milder cases, some small freckle-like or somewhat larger spots may be the only abnormal skin pigmentation observed. Usually, in such milder cases, one or more larger patches are also to be found, but occasionally these are so inconspicuous that they will be overlooked unless they are particularly searched for.

\* Parkes-Weber himself states that when this patient was seen 16 years later, she was found to present a complete characteristic clinical picture of neurofibromatosis. (See *Quart. J. Med.*, 23: 152, 1929-30.)



Furthermore, the abnormal pigmentation seems to show a somewhat different trend in respect to distribution and topography in the two disorders. Specifically, in cases of fibrous dysplasia, the pigment plaques, whether small or large, tend to have an irregular, smeary appearance. In neurofibromatosis,



FIG. 5. A, Photograph of a relatively small, smeary, yellow pigment patch on the outer aspect of the lower part of the left leg of a girl of 9 who has fibrous dysplasia involving the right pubic bone, femur, tibia, and first metatarsal. Histologic examination of skin and subcutaneous tissue from the site failed to reveal any abnormalities except the presence of melanin granules in the basal cells of the epidermis. On the upper part of the chest, anteriorly, a few scattered yellowish pigment spots are also present.

B, Photograph of the back of a girl of 11 affected by neurofibromatosis. The scar in the midline is from a previous surgical intervention for the correction of the scoliosis. Note the extensive pigmentation of the back, which pigmentation, on the left side, extended onto the front of the abdomen and on the right side onto the thigh. A palm-sized area of the abnormally pigmented skin in the right lumbodorsal region showed unevenness of the surface and induration of the deep cutis and subcutis. This was proved by biopsy to be the result of a diffuse neurofibromatous overgrowth (see C).

C, Photomicrograph ( $\times 175$ ) showing details in the pigmented, indurated area mentioned in B. Note the tangled and whorled character of the tissue constituting the local deep cutis and subcutis and typical of neurofibromatous histology.

the plaques or blotches of pigmentation tend to be sharper and somewhat less irregular in outline. Also, in cases of fibrous dysplasia, plaques of pigmentation are more likely to be found on the head, neck, buttocks, and extremities than on the trunk proper, while in neurofibromatosis they definitely predilect the

trunk. In addition, in fibrous dysplasia, the pigment plaque or plaques are not infrequently limited to the side of the body having the major skeletal involvement. Finally, small, freckle-like spots of skin pigmentation constitute only a subordinate part of the skin pigmentation picture [in fibrous dysplasia, when present there at all, while in neurofibromatosis they tend to be a striking feature of the picture (again on the trunk).

To continue, in fibrous dysplasia, the abnormally pigmented skin areas are brown (usually light brown), not raised, and of the same texture as the rest of the skin surface. Those who have studied these pigmented skin areas histologically from biopsy specimens agree that all one notes is an increased melanin content, usually limited to the basal cells of the epidermis, the corium and subcutaneous tissues not being essentially modified. In neurofibromatosis as contrasted with fibrous dysplasia, many of the larger pigmented plaques are decidedly brown, if not dark brown, and many of the freckle-like spots may be so too, though these latter may shade down to a yellowish tone. In neurofibromatosis, too, the pigmentation itself is due to an increased melanin content of the basal cells of the epidermis. However, this fact is not necessarily significant, since, for instance, in Addison's disease, also, the pigmentation of the skin and mucous membranes has this basis. What is significant is that in neurofibromatosis, many of the pigmented skin areas overlie neurofibromata in the skin and subcutis which have elevated the skin in the pigmented area. Indeed, one may encounter pigmented skin plaques which, though not raised, are indurated and otherwise changed in texture, again by underlying neurofibromatosis. On the other hand, in cases of fibrous dysplasia, neurofibromata have never been reported in the corium or subcutaneous tissues as Thannhauser seems to claim (figs. 5A, B, and C).

#### PUBERTAS PRAECOX IN FIBROUS DYSPLASIA VS. NEUROFIBROMATOSIS

The occurrence of various endocrine manifestations—and especially pubertas praecox—in some of the cases of fibrous dysplasia and in some reported cases of neurofibromatosis is likewise offered by Thannhauser as supporting the interrelation of the two conditions. In a broad generalization, these endocrine disorders are attributed in both diseases to “anatomical changes connected with neurofibromatous pathology.”

The one case of fibrous dysplasia cited in this connection which came to autopsy was that previously reported by Freedman, of a girl showing extensive skeletal changes, pubertas praecox, and other manifestations of the disease. In this case, the autopsy failed to reveal any abnormalities of the endocrine glands to explain the pubertas praecox. The only suggestive finding relating to the pubertas praecox was what appeared to be an accessory nucleus in the subthalamic area, apparently representing a congenital anomaly. It is true that, in general, hypothalamic lesions are recognized as being sometimes responsible for the manifestations of precocious puberty. Even allowing for this, however, one would still have to explain in this case how this accessory subthalamic nucleus, by itself, constitutes evidence of neurofibromatous pathology. Indeed,

there is no evidence of the presence of "neurofibromatous pathology" at all in this case, unless one would accept the idea that abnormal skin pigmentation by itself is an adequate pathologic criterion of the presence of neurofibromatosis as a systemic disorder.

In addition to the autopsied case cited above, there is the one reported by Sternberg and Joseph (18). This is the case presenting fibro-osseous skeletal lesions, precocious puberty, abnormal skin pigmentation, and hyperthyroidism which was originally reported mainly on a clinical basis by McCune and Bruch. In this case, a detailed anatomic study was ultimately carried out at the Montefiore Hospital, where the laboratory is headed by Doctor David Marine, whose special interest in the endocrines is well known. No abnormalities were found in the endocrine glands or the ovaries to account for the *pubertas praecox*. The central nervous system and especially the brain, which was studied by Doctor Charles Davison, neuropathologist to that hospital, also failed to show any abnormality which would account for the *pubertas praecox*. After analysis of all the anatomic findings in their case, Sternberg and Joseph state that the exact mechanism underlying the *pubertas praecox* in this patient remains a matter of speculation.

Incidentally, in this case, histological examination of an abnormally pigmented skin area again showed mainly loading of the basal cells of the epidermis with melanin, and certainly no mention is made of anything suggestive of neurofibroma beneath the epidermis. Furthermore, nowhere in the detailed protocol is it mentioned that anything suggestive of the pathology of neurofibromatosis was encountered elsewhere in the body either.

#### SUMMARY AND CONCLUSIONS

We have attempted to show that the skeletal changes observed in cases of fibrous dysplasia, which are of consistent pattern and indeed constitute its central feature, are by no means analogous, roentgenographically or anatomically, with the highly various skeletal changes found in cases of neurofibromatosis.

Furthermore, we have brought out the idea that abnormal skin pigmentation is not necessarily prominent in cases of fibrous dysplasia, except in the more severe cases and notably in those in which *pubertas praecox* and other endocrine manifestations are part of the clinical picture. Also, it was pointed out that the pigmentation in this disorder results from melanin loading, especially of the basal cells, of the epidermis and is never associated with the presence of neurofibromatous overgrowth in the cutis and subcutis as it so often is in neurofibromatosis, in which, furthermore, abnormal melanin deposits in the skin are an almost constant finding.

In addition, the obscurity of the basis of the *pubertas praecox* in fibrous dysplasia was emphasized. Specifically, it was noted that the detailed autopsy study of the case reported by Sternberg and Joseph failed to reveal any anatomic basis for the *pubertas praecox*, and that furthermore there was no indication of the presence of neurofibromata anywhere in the body.

Also, it was pointed out that the hereditary and familial character of neuro-

fibromatosis has been well established, that fibrous dysplasia has shown no such character, and that furthermore the antecedents of patients with fibrous dysplasia show no special prevalence of neurofibromatosis among them.

Altogether, the present writer believes that Thannhauser's efforts to put fibrous dysplasia and neurofibromatosis within a single disease category on the basis of supposedly similar skeletal lesions, abnormalities in pigmentation, and endocrine abnormalities (especially precocious puberty) are misdirected. In the course of these efforts he seems to us to have distorted the essential nature of both neurofibromatosis and fibrous dysplasia. In regard to neurofibromatosis he has done this by playing up the abnormal skin pigmentation as the *sine qua non* of the disease and by playing down the importance and specific character of the actual neurofibromatous lesions and the variety of the skeletal abnormalities encountered (mainly anomalies and developmental defects). In regard to fibrous dysplasia, he has done it by likewise playing up the abnormal skin pigmentation (which is not necessarily prominent in this disorder and has not been found associated with it with dermal and subcutaneous neurofibromata or neurofibromata of nerve trunks) and at the same time playing down the rather distinctive fibro-osseous character of the skeletal lesional tissue, which, in spite of the absence of histologic evidence, he tries to interpret as neurofibromatous in nature. Finally, he neglects the difference between the two disorders which is indicated by the recognized hereditary and familial character of neurofibromatosis in contrast to fibrous dysplasia.

#### ADDENDUM

Though not identifying it with neurofibromatosis, Snapper, too rejects the idea that fibrous dysplasia of bone is a disease entity. He maintains that it is to be linked with Hand-Schüller-Christian's disease (lipoid granulomatosis) as an atypical clinical expression of that disorder. Specifically, he holds that it is atypical clinically because of the absence of damage to the base of the skull in the general area of the pituitary and the consequent absence of exophthalmos, diabetes insipidus and other evidence of pituitary injury. (See: Snapper, *I. Medical Clinics on Bone Diseases*, New York, 1943, pp. 157-171.)

Snapper came to this conception of the nature of the condition which we call fibrous dysplasia of bone on the basis of 3 cases, only 2 of which (case 1 and case 2) the writer would accept as unequivocal instances of fibrous dysplasia in multiple bones. Anatomically, Snapper claims support for his opinion because, in biopsy specimens from these cases, the fibrous connective-tissue substratum of the lesion showed "groups of foam cells" which, by appropriate methods, revealed the presence of "double-refracting fat particles" in their cytoplasm. In case 1, he found these foam cell nests in the initial biopsy specimen, taken from one of the femoral lesions. In case 2, he found foam cells only in the third lesion biopsied,—one in a femur. Previously, in this case, biopsies had been done on lesions in both humeri, but in neither specimen did the tissue examined show the presence of nests of foam cells. Snapper therefore concluded that to demonstrate foam cells in the lesions of fibrous dysplasia (which show, in his

opinion, that basically this lesion is really a lipogranuloma) the biopsy must be taken when the lesion is in an early stage of its evolution, since ultimately the lipid may be crowded out.

That in an occasional lesion of fibrous dysplasia the fibrous connective-tissue substratum may show a few nests of foam cells was already pointed out by Lichtenstein and the present writer.<sup>4</sup> However, this finding alone is hardly sufficient to justify designating such a lesion as a lipogranuloma. Indeed, one can find some nests of foam cells for instance in an osteomyelitic bone lesion, in a giant-cell tumor, in the connective-tissue wall of a solitary bone cyst, and sometimes in an osteogenic sarcoma or fibrosarcoma of a bone, or even in a carcinoma metastatic to a bone. Certainly one would not hold, on the basis of such an incidental or secondary finding, that these various lesions, too, represent lipogranulomas. The nests of foam cells which one finds occasionally in a fibrous dysplasia lesion are small, may be limited to one or a few fields of a large biopsy specimen, and are likewise of an incidental or secondary character. The places where they appear are probably sites of tissue degeneration or hemorrhage, and the foam cells in question here are to be interpreted as collections of macrophages which have absorbed lipid at the site of previous tissue damage.

From another angle, to claim, as Snapper does, that in the "earlier stage of the disease, [fibrous dysplasia or Albright's disease] the bone marrow . . . may well have contained nests of proliferating reticulo-endothelial cells full of cholesterol" which in the later stages of the disease have disappeared, is to express a mere hypothesis. In a given case of fibrous dysplasia, there may be many silent lesions, but these are not necessarily younger than lesions in crucial bone sites (such as the neck of a femur) which have directed attention to the condition because of pain, deformity, or fracture.

In regard to Schüller-Christian's disease, there can be no doubt that it has its basis in a peculiar chronic inflammatory originally non-lipid histiocytosis or reticuloendotheliosis in which the lesions eventually become scarred, collagenized, and lipidized (see Jaffe and Lichtenstein, *Arch. Path.*, 37: 99, 1944). It is also true that in the terminal stages of a case of lipogranulomatosis one may find some skeletal lesions which are so scarified that lipid is no longer obvious in them. However, even these lesions can still be shown to contain some extra- and intracellular lipid, and the great majority of the lesions in any case of Schüller-Christian's disease do contain an abundance of lipid, no matter how strongly the lesions are scarified. Furthermore, in such cases, even if the skull bones and the brain coverings are not involved, one is very likely to find extensive lipid-containing scars in the lungs and pleura, and these may even have led to death through right heart failure. On the other hand, no matter how extensive the skeletal involvement may be in a case of fibrous dysplasia, no one has ever noted, in this condition, the presence of complaints arising from pulmonary scarring.

Finally, one may ask these questions of any one who advocates identification of fibrous dysplasia with Schüller-Christian's disease: In view of the fact that the lesions of Schüller-Christian's disease are irregularly distributed over the skeleton, why is it that the lesions of fibrous dysplasia in multiple foci tend strongly



to have a unilateral distribution and are often even limited strictly to some of the bones of one limb bud? Again, why is it that one sometimes finds, in the lesions of fibrous dysplasia, larger or smaller foci of hyaline cartilage imbedded in the connective-tissue substratum (a finding which has never been recorded in connection with the pathology of Schüller-Christian's disease)? Also, why is it that in frank cases of Schüller-Christian's disease (that is, cases showing even the Christian triad) yellow-brown melanin pigmentation of the skin in the form of plaques, patches, or spots has never been noted, while in pronounced cases of fibrous dysplasia it is almost regularly seen and is indeed considered part of the disease syndrome as a whole?

#### BIBLIOGRAPHY

1. ALBRIGHT, F., BUTLER, A., HAMPTON, A. O., AND SMITH, P.: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females. Report of 5 cases. *New England J. Med.*, 216: 727, 1937.
2. McCUNE, D. J., AND BRUCH, H.: Osteodystrophia fibrosa: Report of a case in which the condition was combined with precocious puberty, pathologic pigmentation of the skin, and hyperthyroidism, with review of the literature. *Am. J. Dis. Child.*, 54: 806, 1937. See also: McCune, D. J.: *Trans. Soc. Pediatric Research*, (May 5, 1936), in *Am. J. Dis. Child.*, 52: 734, 1936.
3. LICHTENSTEIN, L.: Polyostotic fibrous dysplasia. *Arch. Surg.*, 36: 874, 1938.
4. LICHTENSTEIN, L., AND JAFFE, H. L.: Fibrous dysplasia of bone: A condition affecting one, several, or many bones, the graver cases of which may present abnormal pigmentation of skin, premature sexual development, hyperthyroidism, or still other skeletal abnormalities. *Arch. Path.*, 33: 777, 1942.
5. FALCONER, M. A., AND COPE, C. L.: Fibrous dysplasia of bone with endocrine disorders and cutaneous pigmentation (Albright's disease). With a Discussion of the Bone Changes by A. H. T. Robb-Smith. *Quart. J. Med.*, 35: 121, 1942.
6. THANNHAUSER, S. J.: Neurofibromatosis (von Recklinghausen) and osteitis fibrosa cystica localisata et disseminata (von Recklinghausen). A study of a common pathogenesis of both diseases. Differentiation between "hyperparathyroidism with generalized decalcification and fibrocystic changes of the skeleton and osteitis fibrosa cystica disseminata." *Medicine*, 23: 105, 1944.
7. PUECH, A.: a. Les Manifestations Osseuses dans la Neurofibromatose. *Paris méd.*, 15: 502, 1925. b. Friedman, M. M.: Neurofibromatosis of bone. *Am. J. Roentgenol.*, 51: 623, 1944.
8. GOULD, E. P.: The bone changes occurring in von Recklinghausen's disease. *Quart. J. Med.*, 11: 221, 1917.
9. BROOKS, B., AND LEHMAN, E. P.: The bone changes in von Recklinghausen's neurofibromatosis. *Surg., Gynec. & Obst.*, 37: 587, 1924.
10. UHLMANN, E., AND GROSSMAN, A.: Von Recklinghausen's neurofibromatosis with bone manifestations. *Ann. Int. Med.*, 41: 225, 1940-41.
11. JAFFE, H. L., AND LICHTENSTEIN, L.: Solitary unicameral bone cyst. With emphasis on the Roentgen picture, the pathologic appearance, and the pathogenesis. *Arch. Surg.*, 44: 1004, 1942.
12. JAFFE, H. L., AND LICHTENSTEIN, L.: Non-osteogenic fibroma of bone. *Am. J. Path.*, 18: 205, 1942.
13. STALMANN, A.: Nerven-, Haut- und Knochenveränderungen bei der Neurofibromatosis Recklinghausen und ihre entstehungsgeschichtlichen Zusammenhänge. *Virchows Arch. f. path. Anat.*, 289: 96, 1933.

14. PENFIELD, W.: The encapsulated tumors of the nervous system. Meningeal fibroblastoma, perineural fibroblastoma, and neurofibromata of Recklinghausen. *Surg., Gynec. & Obst.*, 45: 178, 1927.
15. BAILEY, P., AND HERRMANN, J. D.: The rôle of the cells of Schwann in the formation of tumors of the peripheral nerves. *Am. J. Path.*, 14: 1, 1938.
16. PARKES-WEBER, F.: Cutaneous pigmentation as an incomplete form of Recklinghausen's disease, with remarks on the classification of incomplete and anomalous forms of Recklinghausen's disease. *Brit. J. Dermat.*, 21: 49, 1909.
17. GRENET, H., DUCROQUET, R., ISAAC-GEORGES, P., AND MACÉ, M.: *Forme Fruste Pigmentaire et Osseuse de la Neurofibromatose.* *Presse méd.*, 42: 2060, 1934.

## THE PATHOGENESIS OF ATHEROSCLEROSIS<sup>1</sup>

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Perhaps no subject is more appropriate for discussion in this anniversary volume dedicated to Dr. Eli Moschowitz than that of arteriosclerosis, the study of which is so closely associated with his name and toward the elucidation of which he has contributed so much over many years of fruitful study. It is our purpose to present a hypothesis for the pathogenesis of atherosclerosis based upon our own studies and an analysis of the literature, in the hope that we may focus attention on the many aspects of this vital subject requiring solution. Our consideration will be confined to atheromatous intimal disease; Mönckeberg's medial sclerosis and arteriolosclerosis will be omitted.

### THE MAGNITUDE OF THE PROBLEM: INCIDENCE AND AGE DISTRIBUTION OF ATHEROSCLEROSIS

There is much evidence that arteriosclerosis is today the leading cause of morbidity and mortality. Yet it does not appear in compilations of mortality causes, and often not even as a subheading in mortality tables. For example, in the 1940 mortality summary (A3), four of the principal causes of death listed include within them a large percentage of arteriosclerosis of the organ in question. Thus, heart disease, the first and chief cause of death in the United States today, taking an annual toll of just under 400,000, probably includes 200,000 cases due to coronary arteriosclerosis. Intracranial lesions of vascular origin, the third major cause of death, responsible for 120,000 deaths, includes an estimated 75,000 resulting from cerebral arteriosclerosis. Kidney disease, the fourth principal cause of death with over 100,000 instances, includes 65,000 resulting from arteriosclerosis, according to 1941 tables (A4). Diabetes, the eighth major cause of death contains at least 15,000 cases due to arteriosclerosis out of 35,000 instances. From such a rough appraisal, it would appear that arteriosclerosis is the leading cause of death, with a total in 1940 of 355,000 victims; yet it is credited in tables with 23,000 deaths exclusive of coronary and renal sclerosis (A4). Joslin (A10) considers the mortality from arteriosclerosis in Massachusetts to be 37 per cent of the total deaths.

Statistical studies of the incidence of arteriosclerosis are handicapped by a lack of agreement on uniform terminology and necropsy standards. It is not settled whether milder degrees of atheroma are "pathological" or what degree of atherosclerosis is needed before it is included in the necropsy diagnosis. Likewise, there is no agreement on criteria for the clinical diagnosis of arteriosclerosis. The use of elevated blood pressure as a diagnostic guide is not acceptable. Any

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figures compiled for its clinical incidence on the basis of palpable arterial thickening or x-ray findings of calcification, are admittedly unreliable. Figures of prevalence rates range from 3.38 to 32.3 per 1,000 population (A14). Obviously, many cases are clinically unrecognized since arteriosclerosis is a slowly developing disease which may be clinically silent for many years, as evidenced by the fact that while the estimated prevalence was 3 per 1000, only  $\frac{1}{3}$  of these were ill (A14). There is, therefore, a real need for some test to measure atherosclerosis during life.

Arteriosclerosis has shown a relative increase in incidence because of the lengthening life span due to better control over epidemic and infectious diseases and infant mortality, which has caused our population to grow older. It would be wrong, however, to interpret this trend as indicating that arteriosclerosis is a disease of the senile and of senescence alone, and that since death must come to all of us, arteriosclerosis finally steps in when other causes have been avoided. Increasing recognition is being given to the fact that arteriosclerosis is also an important disease of the young adult. Using palpable radial artery thickening as a crude guide, males under 35 have been shown to have an incidence of 5 to 10 per cent, while females under 35 have an incidence  $\frac{1}{5}$  as great (A14). In soldiers in World War I, arteriosclerosis was found at necropsy in over 30 per cent of those at 20 years, in over 45 per cent at 25 years, and over 80 per cent at 50 years (A8). In these studies, the finding of arteriosclerosis, chiefly located in the left coronary artery, was an incidental necropsy observation. This observation is being repeated in the present war and in addition, clinical evidence of coronary arteriosclerosis is being observed as well as a number of fatalities (A6). In civilian practice too, arteriosclerosis of the coronary arteries in young persons may result in death (A7).

Careful anatomic examination shows that the earliest stage of atherosclerosis begins in infancy, progressing and extending during childhood and adolescence (A1, A9, F17). In fact, the high incidence of these earliest fatty lesions has led some to consider them a normal occurrence. Recent careful studies, however, indicate that they are pathological and the antecedents of the later full blown atherosclerosis (A9). These early atheromatous plaques occur in 5 per cent of infants under 6 months and in almost 100 per cent of children over 8 years (A9). While some of these yellow streaks are possibly reabsorbed (A1, F18), the increasing incidence with age reveals that the main tendency is toward progression (A9).

It is obvious that arteriosclerosis, considering its importance, has received far too little attention from the financial and public educational campaigns of public and private agencies. In the future, increasing emphasis will undoubtedly be placed upon arteriosclerosis and more support must be given to investigations of its pathogenesis, leading to its early recognition and prevention.

#### HISTORICAL DEVELOPMENT OF KNOWLEDGE OF ARTERIOSCLEROSIS

(a) *Stage of Pathological Observation:* Evidences of arteriosclerosis have been found in Egyptian mummies. It has been estimated that it was almost as com-

mon a disease among the upper class Egyptians as it is among us today. Lesions such as calcified aortas and iliac arteries, and calcified plaques and thrombi on old atheromatous ulcers were common findings (B1).

While calcified heart lesions were first recognized as early as the 16th century, descriptions of calcified arteries did not begin to accumulate until the 17th century. Harvey, Bartholin, and Malpighi all mentioned arteriosclerosis. In the 18th century localization of lesions became more exact. As early as 1740, it was recognized that hardening of the coronary arteries could occur at all ages (Crell). That arteriosclerosis is not an inseparable part of the aging process was demonstrated by the description of a 91 year old woman without arterial change (Morgagni, 1761). Arteriosclerosis was recognized as a true disease, not simply a natural aging process by Hodgson in 1815, and in 1829 Lobstein coined the term arteriosclerosis.

A number of observations were made on this subject in the 19th century and the opening up of the new field of cellular pathology led by Virchow initiated tremendous strides in the histologic study of the disease. One of Virchow's pupils, Rindfleisch, recognized two forms of lesions: the first, initiated by connective tissue thickening of the intima; the second by fatty change of the intima. Both might lead to the more advanced lesions.

By the end of the 19th century, the vascular background of many disorders was recognized and these disorders were clinically diagnosed. The distinction between syphilitic arteritis and arteriosclerosis was increasingly established. Blood pressure measurement became a common clinical practice and its relation to arteriosclerosis came under consideration. The term atherosclerosis was coined in 1904 by Marchand, and in 1911 Klotz differentiated medial sclerosis from other arteriosclerotic lesions.

(b) *Stage of Chemical and Experimental Investigation:* The next great advance in the knowledge of the pathogenesis of arteriosclerosis came with the introduction of chemical analysis and animal experimentation. We are still in this stage.

(1) *Agents other than cholesterol:* The experimental work with animals first concerned itself with attempts to produce arteriosclerosis by local arterial injuries of a mechanical, toxic, or infectious nature. Experiments with ligating, pulling or pinching; experiments with electric and chemical cauterization; experiments with injection of various irritating chemicals, or the injection of bacteria and their toxins succeeded in producing inflammatory lesions of the arterial wall but no intimal atherosclerosis (C2). Recent attempts in the same direction, namely the ligation of arteries, the injection of streptococcus viridans, silica, tubercle bacilli, and even cholesterol resulted in granulation tissue, inflammatory exudates and medial degeneration but no intimal atheroma (C35, C36). Chronic sepsis, lead, nicotine and a number of acids failed to produce atherosclerosis in dogs (C1). Diffuse hyperplastic vascular lesions were reported from the combined effects of diphtheria toxin and vitamin C deficiency in guinea pigs (C32). Repeated injections of horse serum may cause coronary arteritis (C11, C38). Digitalin, caffeine, nicotine, and theocin likewise cause inflammatory lesions (C2). Mercuric chloride (C20), uranium nitrate, (C7, C9) and tyra-



mine (C10) lead to medial necrosis. Viosterol in massive doses leads to medial calcification (C13, C14, C16, C42, C43) which may be accompanied by intimal fibrous proliferation (C17). Section and stimulation of the nerves of the arteries has been reported to produce inflammatory arterial change (C2) but no lesions resembling atherosclerosis.

The injection of adrenalin (C2, C34) or large doses of thyroxin (D26, D54) produces so-called adrenalin sclerosis which is characterized by medial degeneration, calcification and even aneurysm formation.

Local mechanical and toxic injuries increase the local permeability of the arterial wall to dyes, stains and also to cholesterol when the injury is accompanied by cholesterol feeding, according to Anitschkow (C2). On the other hand, systemic chemical and toxic substances given to rabbits and cats simultaneously fed cholesterol, with a view to injuring the vessel wall and increasing permeability to cholesterol, were without effect (C29). Streptococcus toxin, ammonium chloride, artificial fever, peptone injections, horse serum, histamine and uric acid failed to accelerate or increase cholesterol atherosclerosis (C29).

Blood pressure changes alone among physical forces have been reported as producing atherosclerosis. Although Klotz' early report of producing atherosclerosis in rabbits by hanging them upside down was not confirmed (C2), rabbits with renal hypertension caused by constriction of the aorta proximal to the renal arteries do develop atheroma of the aorta proximal to the constricting clamp (C6). Similarly, elevating the blood pressure by keeping rabbits in the upright posture in association with cholesterol feeding accelerates and exaggerates the development of atherosclerosis (C44).

On the other hand, lowered blood pressure has likewise been claimed to favor atherosclerosis. Lowering the pressure by feeding nitrites to rats was reported to lead to intimal thickening (C27), but no mention of atheroma development was made.

Aside from tension changes, irradiation is the only physical agent reported to produce atherosclerosis. Intimal atheroma in human radiated arteries has been described by Sheehan (C40).

Only with irradiation and increased tension has any clear evidence been presented to point to a rôle of physical agents in the development of intimal atherosclerosis. All other factors to date have been unsuccessful aside from cholesterol.

(2) *Experimental cholesterol atherosclerosis*: Aschoff and his school are responsible for the first chemical studies of aortas and arteriosclerotic lesions and the resultant recognition of cholesterol as the fundamental chemical constituent of the lesions. Their histologic studies too identified cholesterol in the lesions by its doubly refractive quality.

It is now established that the cholesterol content of the aorta increases with aging, independent of atherosclerotic lesions (D29, F23) but that the amount of cholesterol in the aorta likewise parallels the degree of atherosclerosis (D29, F24). An old normal aorta shows more cholesterol than a young normal one (D29, F20), while the lesions themselves show a far greater increase in cholesterol

(F20, F24). Recent studies (D29) confirm these findings and show that calcium likewise increases in the aorta, particularly in the media, with age (D29, F3, F10) and that calcium is present in the earliest intimal atheromatous lesions before it is visible (D29). The composition of the lipids of the intimal atherosclerotic plaque is essentially the same as that of the blood plasma (D29, F20, F24).

In 1911, Anitschkow (D2) found that lesions resembling human arteriosclerosis could be produced in rabbits by feeding them pure cholesterol dissolved in vegetable oil. Sometime later it was reported (D33, D67, D75), and we have recently confirmed it (D15, D16), that the same thing can be done in the chick. Anitschkow's work opened new vistas to the study of the pathogenesis of atherosclerosis and has been confirmed by hundreds of workers. Feeding large amounts of cholesterol to rabbits or chicks for several months causes a tenfold or more elevation of the serum cholesterol and extensive deposits of cholesterol in many organs, as well as marked degrees of extensive intimal atherosclerosis. Furthermore, in rabbits, feeding small amounts of cholesterol over much longer periods results in atheroma without any accompanying elevation of serum cholesterol (D2).

In the guinea pig, cholesterol feeding fails to produce gross atherosclerosis although marked elevations of serum cholesterol and marked accumulations of cholesterol in various organs result; only microscopic atheroma can be found (D5, D14). In cats (D74), dogs (D7, H60) rats (D14, D74, H58) and mice (D43, D73, D74) cholesterol administration fails to elevate the serum cholesterol in comparable degree (3 times compared to 20 times (D14)) and fails to result in gross atherosclerosis (D20). It appears, therefore, that the rabbit has a special susceptibility to the development of hypercholesterolemia and atherosclerosis when fed cholesterol. This cannot be a characteristic of herbivores in general, since in guinea pigs no gross cholesterol atherosclerosis has ever been reported. Nor are there reports of such experimental lesions in any other herbivore. (If microscopic atheroma is accepted as a criterion of successful experimental lesions, then there are similar successful reports of lesions in dogs and mice. From our point of view, gross atheroma is necessary for a successful experiment.) Hence the rabbit is not an example of all herbivores but only of the rabbit. Similarly, rats and mice which are not susceptible to cholesterol-feeding atheroma are not characteristic of all omnivores. In the chick, an omnivore, cholesterol feeding readily results in atherosclerosis. The oft-repeated contrast of herbivores and omnivores should be dropped when it is recognized that a herbivore and an omnivore may be more alike in respect to experimental atheroma than two omnivores or two herbivores.

In recent years, an increasing skepticism has developed concerning the significance of the cholesterol feeding experiments, partly because of the failure to confirm them in many species and partly because of the failure to find hypercholesterolemia in man regularly associated with atherosclerosis, and the inability to produce hypercholesterolemia in man after feeding cholesterol. Therefore, there has appeared to be little connection between the human disease and

the experimental disease except the similarity of lesions. Report after report points out that because of the herbivorous nature of the rabbit, cholesterol is a foreign food for this species and that this dissimilarity to man makes the production of lesions possible.<sup>2</sup> The demonstration that cholesterol feeding in the chick produces atheromatous lesions answers this objection and signifies that the work on the rabbits has been an important contribution. The chick is an omnivorous animal which, like man, does normally ingest cholesterol and which does in nature develop humanlike atherosclerosis (A17, A18, A19). The lesions produced in chicks by diets high in cholesterol are almost identical with the spontaneous lesions found in this bird at an older age (D15, D16).

The work on cholesterol feeding of rabbits and chicks is of significance in the study of the pathogenesis of human atherosclerosis since it is the most consistent method developed for the production of experimental lesions and the study of their prevention or modification.

#### FACTORS AFFECTING EXPERIMENTAL CHOLESTEROL ATHEROMATOSIS

1. *Thyroid, Iodides, Thyrotropic Factor of Pituitary, Thiocyanate*: The simultaneous administration of whole thyroid gland, or potassium iodide, or organic iodide with cholesterol prevents experimental atheromatosis (D54, D55, D61). Thyroxin fails to do this effectively (D61). The protective action of potassium iodide depends on the presence of the thyroid gland, since after thyroidectomy it is ineffective in preventing atheromatosis (D65). Furthermore, rabbits refractory to experimental atheroma can be made susceptible by thyroidectomy (D58, D66). Iodides do not affect removal of lesions produced by earlier cholesterol administration (D50).

There are apparently two different actions of thyroid, one on the blood cholesterol level and the other on the arterial intima. For organic iodide may prevent atheroma without preventing hypercholesterolemia (D55). Although potassium iodide prevents both hypercholesterolemia and atherosclerosis for several months, after this the blood cholesterol rises and yet atherosclerosis does not develop (D62). Furthermore, potassium iodide given after the blood cholesterol is elevated will cause a further rise and will retard the drop in blood and adrenal cholesterol which usually supervenes after the administration of cholesterol is stopped (D62, D63, D66). In thyroidectomized rabbits which are fed both cholesterol and potassium iodide, the administration of thyroid or thyroxin will delay but not prevent the rise in blood cholesterol (D62). Yet even with hypercholesterolemia, these rabbits have very little atherosclerosis (D62). Hence thyroid appears to be related to the local accumulation of cholesterol as well as to the serum level (D55, D66). It may influence the site of lesions according to Goormaghtigh and Handovsky (C13) who found that vita-

<sup>2</sup> It is frequently stated that since the rabbit does not normally ingest cholesterol it does not ordinarily absorb any sterol because plant sterols have been assumed to be unabsorbed following the work of Schönheimer. Even this view may be changed as recent work (H52) suggests that sitosterol may be absorbable after all.

min D affected different coats of the artery depending on the presence or absence of the thyroid gland.

While the thyroid gland secretion tends to prevent the development of cholesterol atherosclerosis, the thyrotropic hormone of the anterior pituitary favors its development (D9). Yet both thyroid (D62, D66) and thyrotropic hormone (D64) tend to lower the serum cholesterol level. As with other functions, these two hormones may exert antagonistic effects on intimal cholesterol lesions. With hypofunction of the thyroid, the failure of an antagonist mechanism may result in hyperfunction of the pituitary thyrotropic hormone which favors the development of atheroma. However, thyroidectomy by itself without cholesterol feeding does not produce atheroma in rabbits (D65). The administration of thyroid or of iodides (in the presence of thyroid) may counteract the thyrotropic hormone and inhibit atherosclerosis regardless of the serum cholesterol level.

Potassium thiocyanate, on the other hand, is reported to prevent atheroma in cholesterol-fed rabbits in the absence of the thyroid (D46). The fact that thiocyanate often results in enlargement of the thyroid gland with the production of hypothyroidism, which may be counteracted by thyroid administration (H50), suggests that it may act through the thyroid-thyrotropic mechanism.

The thyroid-thyrotropic effect on atherosclerosis in the rabbit may act through a change in rate of cholesterol transport. Such a change in rate may reflect either a decrease in local intake or an increased output of cholesterol by the intimal cells, in which it may be present (since apparently all body cells contain cholesterol).

Not only the thyroid stimulating hormone of the anterior pituitary but posterior pituitary extract as well acts to enhance the development of cholesterol atherosclerosis in rabbits (D51, D52).

2. *Sex Hormones*: The rôle of sex hormones in experimental atherosclerosis has only begun to be investigated. Castration has been reported to increase the degree of atherosclerosis in cholesterol-fed rabbits (D53, D58) and to make possible the production of microscopic atherosclerosis in mice (D43). It has been repeatedly observed that rabbits vary in their susceptibility to cholesterol atherosclerosis (D31) and, according to Turner and associates, it is in male rabbits that the failures to induce atheroma chiefly occur (D63). If there is any protective effect from androgens which is removed with castration this has yet to be demonstrated. On the other hand, it has been shown that the administration of either male or female sex hormones to female rabbits will prevent both hypercholesterolemia and atheroma in the presence of the gonads (D45). After gonadectomy of the female rabbit, the hormone administration is ineffective in preventing atheroma (D10), just as it is in the male rabbit before gonadectomy. How these observations tie in with the rôle of the thyroid in the regulation of cholesterol deposits remains to be clarified. It is possible that the sex hormones too have a place in the thyroid hormone—thyroid stimulating hormone inter-relationship.

3. *Lipotropic substances: lipocaic, choline, lecithin*: In the rabbit, the effect of

administration of lipocaic simultaneously with cholesterol on the development of hypercholesterolemia and atherosclerosis is variable. According to some investigators (D30) it may prevent both. No such effect was found in rabbits by others (D19, D69) but a definite protective effect of lipocaic in diabetic dogs was reported (D18).

With choline too, the literature shows conflicting reports which would suggest that some additional factor which is not recognized at present is operating. Steiner (D59) found that choline administered with cholesterol delays, although it does not prevent, the development of hypercholesterolemia and atherosclerosis. On the other hand, Bauman and Rusch (D6) and Himsworth (D28) failed to find any preventive action by choline. According to Steiner (D60), choline may likewise favor the resorption of lesions, while Himsworth (D28) failed to confirm this.

Lecithin, another lipotropic substance, has been found to restrict hypercholesterolemia and to diminish the incidence of cholesterol atherosclerosis in the rabbit (D37, D48). However, this substance raises the blood cholesterol when fed to dogs (H16).

4. *Neutral Fat:* Apparently fat is necessary for optimal absorption of cholesterol. Thus, cholesterol without fat is far less effective in elevating serum cholesterol levels in rabbits (D2) and may be entirely unabsorbed in the rat (H12), although the guinea pig can absorb large amounts of cholesterol on diets containing little fat (H12). Furthermore, the percentage of fat in the diet may influence the effect of cholesterol (H13). Neutral fats aid absorption and may cause reabsorption of cholesterol excreted into the lower bowel (H7). High fat intake may likewise influence cholesterol metabolism secondarily through its goitrogenic effect, since high fat, high protein diets are goitrogenic for rabbits, poultry and brook trout (H41). Fats free from iodine may be especially goitrogenic for pigeons (H41).

5. *Protein:* The protein in the diet may also alter the effectiveness of cholesterol for the production of atherosclerosis in the rabbit (D48). A smaller quantity of cholesterol seems effective in rapidly producing atherosclerosis when it is given in the form of meat, eggs or milk than when pure cholesterol is given (D12, D48). While a high protein soya meal diet from which lipid is extracted fails to produce lesions (D28), a defatted high protein casein diet will (D48). In mice, protein plus cholesterol has been reported to result in microscopic atheroma (D43), whereas cholesterol alone does not produce even microscopic lesions.

6. *Miscellaneous other substances:* Thiamin chloride, ascorbic acid and tocopherol have been tried and found ineffective in the prevention of cholesterol atheroma in rabbits (D24). Alcohol (D22), bromides (D61), and chlorophyll (D46) have likewise been reported ineffectual.

7. *Macromolecular Substances:* The possibility that the large size of the lipoprotein (cholesterol-protein) aggregate may be an important element in the development of the intimal lesions is supported by the investigations of Heuper (C21-C25, G3). He found that intravenous and intraperitoneal injections of



polyvinyl alcohol, a macromolecular colloid (and other macromolecular substances) cause atheroma-like lesions in the large arteries of the dog, morphologically similar to cholesterol atheroma of the rabbit. The foam cells in the intima in these cases contain polyvinyl alcohol (or other substance used) and not cholesterol.

#### GENESIS OF EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS

A number of views have been advanced regarding the genesis of experimental atherosclerosis due to cholesterol feeding. Anitschkow (D2) believes with Virchow and Aschoff that the deposition of lipid is of an infiltrative nature, that lipid enters the intima with the plasma directly from the vessel lumen, wherever the internal elastic lamina has been torn. In the ground substance of the intima, the lipid then undergoes precipitation and secondary calcium deposition may occur. Lipid is extracellular at first according to this view. After reparative fibrous intimal thickening occurs, no further lipid enters the intima. Anitschkow points out that both focal lesions of the arterial wall, inflammatory or other, and elevated blood pressure predispose to the condition by weakening the internal elastica. He believes that these processes in the rabbit are analogous to those occurring in man.

Duff (D21) contends that the primary changes in cholesterol-fed rabbits are necrosis of muscle cells of the media and swelling of the ground substance of the intima. Lipid infiltration is secondary and the earliest lipid is extracellular. Later wandering cells appear, becoming foam cells, and still later fibroblasts may make their appearance. Infiltration of lipid occurs only at sites of local injury, either in the intima or media.

Leary, in his earlier work (D40), described the first change in arteriosclerosis as mucoid degeneration with extracellular isotropic lipid occurring in the intima. This is followed by the appearance of foam cells containing anisotropic lipid, the foam cells arising from monocytes. But in later reports Leary (D41) contends that (a) lipid accumulation is the primary change in atheroma and precedes any degeneration, and (b) the lipid is intracellular from the start. In this latest view, Leary's hypothesis is that cholesterol-laden foam cells (globular lipophages), originating from the Kupffer cells of the liver and the reticulo-endothelial cells of the adrenal, spleen and bone marrow, are liberated into the blood stream after cholesterol feeding in the rabbit. (Similar cells may arise from the brain after injury or from areas of infectious exudate.) These foam cells can be seen in the hepatic veins and in the pulmonary capillaries. They lose some of the cholesterol and decrease in size in their passage through the lungs. Leary reports that they penetrate the endothelium of systemic vessels and accumulate under the endothelium forming atheromatous plaques. "Chemotaxis" is the mechanism for focal penetration, and local mechanical stresses help to determine the precise distribution of lesions. Fibrolipophages appear later and may remove some of the lipid and determine the ultimate form of the lesion (F18).

According to Hueper's views (G3), lesions result from macromolecular substances in the circulating blood stream which form a film over the vessel lining

and interfere with nutrition and oxygenation of the vessel wall. Endothelial cells engulf this material and proliferate to form plaques. Such endothelial cells may migrate to the media. He attributes localization to static mechanical forces resulting from posture and to decreased flow in the vasa vasorum occurring through hypertonus or hypotonus of the blood vessel wall. This view assumes that the endothelium is phagocytic and is involved in the lesions in contrast to other views that it remains intact. Others (D3, D38) have likewise considered the endothelium phagocytic.

We have arrived at certain conclusions as a result of our work with the chick (D16). Our observation of intimal vasa vasorum containing large clumps of foam cells has indicated to us that the vascularization of the arterial wall is a determining factor in the development of atheroma. Foam cells within these vasa, either coming from distant sites of origin or locally produced, may accumulate and interfere with intimal nutrition. We have observed foam cells within the sinusoids of the liver and in the central hepatic veins in the cholesterol-fed chick (D16), as has Leary in the rabbit (D41). Such cells have also been seen crowding lung capillaries. This evidence would suggest that foam cells may originate in the reticulo-endothelial system of the cholesterol-fed chick (and rabbit) and travel through the veins to the arterial circulation and lodge in the vasa vasorum. The possibility that such cells may originate locally cannot be excluded without further evidence. According to our view, lesions may be expected to develop where (a) there are intimal vasa vasorum present to become obstructed and (b) where the number of vasa is critical for the local needs. Portions of the aorta which are uninvolved might be free of atheroma either because (1) there are no intimal vasa or (2) there are so many vasa that obstruction of a few does not seriously interfere with local nutrition. In the rooster, atheroma is most apt to develop in the abdominal aorta at the site at which the intima undergoes physiological thickening with maturation (D16, A17). Presumably, where the intima thickens, new vasa develop and the presence of these intimal vasa may facilitate the development of atheroma by the mechanism suggested above.

#### A CONCEPT OF THE PATHOGENESIS OF HUMAN ATHEROSCLEROSIS

The rôle of the experimental work on cholesterol atherosclerosis in elucidating the pathogenesis of human arteriosclerosis should now be assayed.

1. *Rôle of Cholesterol:* The experimental evidence which has been summarized clearly reveals that cholesterol and its esters, and calcium as well, are the essential primary constituents of atheroma and, at present, that cholesterol feeding is the only consistent method of producing atherosclerosis experimentally. The difficulty in reconciling these facts with human atherosclerosis lies in (1) the absence of hypercholesterolemia in most cases of arteriosclerosis in man and (2) the absence of alimentary hypercholesterolemia in man.

The newer work on human cholesterol metabolism removes some of these difficulties. In the first place, it has been shown that the normal human serum cholesterol level covers a wide range (from 132 to 392 mgm. per cent), wider than

the range for most blood constituents (H55). But the cholesterol level is fairly constant in a given individual in health. Thus a level of 300 may be normal for one individual, but abnormal for a man who has always had a level of 150 (H56). Levels in the upper part of the normal range in individuals with arteriosclerosis may actually be abnormal for the individuals in question.

A survey of clinical studies shows that elevated serum cholesterol content favors atherosclerosis but is not essential for its occurrence. Similarly, elevated serum cholesterol is not always accompanied by atherosclerosis. This is also true experimentally. In man, the lack of correlation between atherosclerosis and the serum cholesterol level has been shown by Lande and Sperry (F14). Lipoidosis may occur without hypercholesterolemia (H62) and, contrariwise, elevated blood cholesterol (as in cretinism (H68)) may occur without lipid deposits (H56). On the other hand, in diseases with known elevation of serum cholesterol, there is an increased incidence of atheromatosis, viz. diabetes (A2, A5, A13, F8, F31), myxedema (F5, H41), and glomerulonephritis (F29, H4, H27, H61). In the xanthomatous diseases, coronary atheroma is found in those with elevated serum cholesterol but not in those with normal serum levels (H62). Recently it has been shown that patients with coronary sclerosis have a definitely elevated average serum cholesterol and that the level shows wider fluctuations than in normals (F27). Furthermore, the mean level of blood cholesterol is higher in cases with arteriosclerosis obliterans of the legs than in the controls, although the range of values is the same in both (F2).

Serum cholesterol levels do not necessarily reflect the cholesterol content of the body tissues, a situation common to other substances, as for example, vitamins. The serum cholesterol level reflects a balance between the rate at which cholesterol enters the blood from depots, from sites of synthesis or exogenous sources and that at which it leaves the blood to be excreted, destroyed or stored. Thus, the rate of transport rather than absorption and excretion determine serum cholesterol levels (H56). Furthermore, the serum level may vary with shifts of cholesterol between red corpuscles and plasma as occurs, for example, with variation in acid-base balance (F29, H37). A rise in whole blood cholesterol may mean a transfer from tissues to blood, whereas a rise in serum cholesterol may mean a shift from red corpuscles to serum. The thyroid and pituitary glands may regulate the shift from tissues to blood in man as in experimental rabbit atheroma. Thus the serum cholesterol elevation in hypothyroidism may be due to an increased uptake from tissue depots or to a decreased output to the tissues. Evidence in animals (D25, H24) suggests that the total body cholesterol does not change after thyroidectomy but that there is a change in its distribution. On this basis, if cholesterol is a major factor in human atherosclerosis, it is not the level of this substance in the serum which is important, but rather the rate of its transport. High rates of cholesterol exchange may be balanced so that the serum cholesterol level is average, high or conceivably even low. Our attention therefore must properly be placed on the rate of cholesterol exchange; and to this end it would be appropriate to develop for clinical assay a "cholesterol tolerance test." Evidence already exists that cholesterol

tolerance varies with body weight, i.e., the obese person responds to a fat meal with a rise in serum cholesterol while the lean one shows a flat curve (H23). Correlations with such a test may reveal a definite trend between arteriosclerosis and "cholesterol intolerance."

2. *Dietary Factors Influencing Cholesterol Metabolism:* (a) *Cholesterol:* The marked species difference in the effect of ingested cholesterol has been discussed earlier. Little direct knowledge is available on the effects of long term cholesterol feeding in man. The administration by mouth of large quantities of cholesterol for a few feedings or for 2 to 4 weeks fails to raise the serum cholesterol (H28) but its administration with lecithin as egg yolk may raise serum cholesterol (H57, H60). Indirect information on dietary cholesterol may be obtained from a comparison of diabetes in the pre-insulin and insulin eras and by an analysis of populations with different dietary habits. The diabetic today with a moderate or low fat diet has a lower serum cholesterol than in the pre-insulin era when high fat diets were in vogue (F11). Omission of all eggs from the diets of diabetic children may lower the serum cholesterol level (F11) but an egg rich diet does not raise it. While the well-controlled diabetic child has a serum cholesterol level in the normal range, it averages significantly above the average level of the non-diabetic child (F13). In some cases of lipoidosis, removal of all cholesterol from the diet (by a strict vegetarian diet) lowers the serum cholesterol (F28).

Few documented reports are available on the comparative serum cholesterol levels of Eskimos with their high meat diet, Europeans and Americans on their rich cholesterol-containing diet, and the Chinese and Arabs on a low meat or meat free diet. It is stated, however, that Eskimos do not have an elevated serum cholesterol (H15); the Chinese (F26) and Japanese (D53) are said to have a low serum cholesterol content and a low incidence of coronary arteriosclerosis (F26). In this connection peptic ulcer patients with their high cholesterol milk and cream diet do not have a greater incidence of coronary sclerosis (F25), but two European explorers on a pure meat diet for a year did show an elevation of serum cholesterol (H63).

The evidence to date, however, does not exclude the possibility that dietary cholesterol may contribute to the development of human atherosclerosis. In fact, the normal serum levels may include an element of alimentary cholesterolemia resulting from the relatively rich cholesterol diet of Americans. Furthermore, studies of serum levels do not exclude the rôle of dietary cholesterol on body stores and transport of cholesterol. It is conceivable that, in man, as in the rabbit (D2), long-term consumption of cholesterol in moderate quantities may favor the development of atheroma without hypercholesteremia. Perhaps the elimination of dietary cholesterol may prove to be one of the more readily controllable of the several factors involved in human arteriosclerosis. But this judgement must be postponed to await more positive evidence.

There is evidence from studies on experimental atherosclerosis and on cholesterol metabolism that other factors of the diet than cholesterol may play a rôle in human atherosclerosis. In this field also, much still remains to be solved. From the evidence at present available certain facts seem clear.

(b) *Fat*: Natural food sources of cholesterol contain neutral fats and lecithin also. There is a fairly constant ratio between total cholesterol and total fat in the plasma (F24, F29). The elevations of serum cholesterol in diabetes (F11), lipoidoses (F28), and in arteriosclerosis obliterans (F2) are associated with elevations of the other lipid fractions and fatty acids. Similarly, the increase in cholesterol content of the aorta with age and atheromatosis is associated with an increase in all lipids and the ratio of one lipid to the others tends to be the same as in plasma (F9). A rise in serum cholesterol follows the administration of lard, butter, vegetable fats to obese persons but not to thin ones (H23). In the thin person, there may be a rise in non-cholesterol lipids, however (H23). Furthermore, obese persons tend to have a higher fasting serum cholesterol level than lean ones (F29, H23).

(c) *Protein*: In experimental atherosclerosis, the protein in the diet may influence the effectiveness of cholesterol in producing lesions (D48). In the plasma, cholesterol is combined with euglobulin and with fibrinogen (H7). It is known that there is a tendency for serum protein and serum cholesterol to deviate in opposite directions as in nephrosis (H61), plasmapheresis (H1) and after hemorrhage (H42).

3. *Endogenous Factors Affecting Tissue Cholesterol Level*: It is clear from experimental work that the thyroid gland plays an important rôle in the development of cholesterol atherosclerosis. There is supporting clinical evidence for this influence in the fact that the serum cholesterol usually rises in hypothyroidism and that this rise can be reversed by thyroid gland administration (H68). Leary (H35) has suggested that as persons grow older the thyroid may function less well. It has been found that persons with atherosclerosis over 55 years of age have lower basal metabolic rates than those without arteriosclerosis (F5). However, there is no direct correlation between the basal metabolic rate and serum cholesterol level, and it is evidently some other property of the thyroid secretion than its calorogenic effect which may be involved. More work along this line is needed. Of interest in this connection is the antagonistic action of thyroid-stimulating-hormone of the pituitary gland to the thyroid hormone on experimental atherosclerosis (D9, D64).

The rôle of the pancreas in the development of atherosclerosis is suggested clinically as well as experimentally (D18) by the greater prevalence of arteriosclerosis in diabetic persons compared with non-diabetics in the various age groups (A2, A5). The details of its possible mode of action are not known. It is clear that the degree of the arteriosclerosis is not proportionate to the severity of the diabetes (F11). Nor is there any relation between blood sugar level (F31) or insulin administration and serum cholesterol (F11, H32). However, the serum cholesterol is often elevated in the presence of ketosis, and always in coma, and drops rapidly as acidosis is successfully treated (F31).

The rôle of the sex glands in arteriosclerosis has been considered by the workers in this field, and the experimental evidence is suggestive. The subject still needs investigation. It is known that in man arteriosclerosis causes more disability in the male than in the female as far as coronary artery involvement is concerned (A4). During puberty, serum cholesterol has been found to rise



temporarily (F31). A rise in serum cholesterol has also been found during the mid-portion of the menstrual cycle and in pregnancy (H7). Sex may operate in indirect ways through the pituitary and thyroid glands rather than directly through the control of the gonads on tissue cholesterol metabolism.

4. *Local Cell Metabolism of Cholesterol:* The rôle of the local cell in the metabolism of cholesterol remains a controversial subject. Cholesterol is present in all body cells; cholesterol esterase is likewise present throughout the body as well as in the blood. It has been suggested that cholesterol-dehydrocholesterol plays a rôle as an oxidation-reduction system in cell metabolism (F28). The work of Schönheimer and Rittenberg with deuterium indicates that cholesterol is slowly synthesized from multiple small molecules (H54) such as acetic acid (H6). Bills (H3) believes that cholesterol originates in the cells in which it is found.

Thannhauser (H62) outlines the possible disturbances in cholesterol intermediary metabolism which may lead to local accumulation in cells: (1) Retention and storage in local cells due to (a) diminished destruction of cholesterol, (b) decreased excretion, or (c) lack of esters or phospholipid. (2) Increased synthesis of cholesterol by cells generally or by reticulo-endothelial cells. He accepts the last as basic in xanthomatosis and points out that once formed, foam cells can increase and migrate. Primary xanthoma is due to intracellular overproduction in his opinion, whereas in the secondary xanthomatosis of diabetes, the lesions are due to retention storage. According to Sperry (H56) local accumulation may be caused by lack of lipolytic enzymes necessary for interchanges among lipids. This would fit in with Leary's views regarding reversibility of atheroma due to adequate lipolysis in youth and the permanence of atheroma due to inadequate lipolysis in older persons (F18). On the basis of histologic studies Hirsch (F10) believes that foam cells develop from normal endothelial cells and that the cholesterol and calcific granules may be produced in these cells.

If this view is supported, future studies must be directed to the factors which lead to local alterations in cell metabolism which enable these cells to accumulate cholesterol. This view at present does not define the factors which cause the local overproduction or retention of cholesterol and determine the site of lesions.

5. *Excretory Factors:* It is not enough to consider the intake, transport and storage of cholesterol in attempting to evaluate its rôle in atherosclerosis but consideration must be given to its excretion and destruction, since disturbances here may be responsible for its accumulation in the body tissues.

Cholesterol is excreted into the large intestine (H7). It is also excreted by the liver in the bile (H5), but this cholesterol is reabsorbed. Colon bacilli in the large intestine may destroy cholesterol to a varying extent so that measured experiments on excretion have been challenged (H61, H62).

6. *Factors Influencing Localization of Lesions:* As is well known, atheroma is not a diffuse lesion but occurs as localized plaques, most often in the descending thoracic aorta at the origin of intercostal arteries, in the abdominal aorta particularly at points of branching such as the bifurcation, and in the coronary arteries.

Those recent experimenters who have adopted the view that imbibition from the plasma is the basic mechanism for atheroma, have offered varied explanations for the development of the localized accumulations. The following are the chief views propounded: (1) Lipid infiltrating diffusely into the vessel wall, gravitates or is massaged by the vessel pulse through the intimal tissue space and is trapped in those sites which are immobile or where scarring obliterates the intimal "tissue space" by joining intima to media, and collects there to form the focus of atherosclerosis (D72). The development of intimal fibrosis and atheroma at the edge of a fixed portion of an artery has recently been demonstrated (D72). However, Harrison (C18) found that the more mobile portions of arteries are susceptible to atheroma. (2) Lipid infiltrates diffusely into the intima in systole and is expressed in diastole by the elastic recoil of the internal elastic membrane except where (a) the elastica is damaged or torn as by excess stress, (b) the intima is too thick for adequate expression, or (c) the intima undergoes some chemical change which makes it bind the lipid (F23). (3) Lipid infiltration occurs in greater amounts in those regions where stress and stretching injure the ground substances of the intima (F9) or have damaged the media (D21) or the elastica (D2).

All of these hypotheses are based on the assumption that the lipid deposit is on a purely mechanical basis of preferential filtration. They are based in part on observations of extracellular lipid and intimal or medial degeneration in small lesions assumed to be the earliest changes. Duff (D21) claims that the first visible microscopic change is degeneration and necrosis and only later does extracellular lipid appear, to be followed still later by foam cells. However, careful histologic studies by others (D41, E7, E12) have shown the earliest lesions to be subendothelial foam cells containing anisotropic lipid or cholesterol. If lesions go through cyclic changes as has been indicated (F18), these conflicting views may mean that the last stage of a subsiding lesion, after foam cells have degenerated and lipid has been liberated, is mistaken for the first stage of a beginning lesion.<sup>3</sup> No positive experimental evidence of infiltration has been produced.

Opposing the theory of infiltration is that of local production of lipid in the lesion. According to this view, advanced by Hirsch (F10), the continuous vibration or agitation of the arterial wall, more marked at sites of eddies, breaks up the internal elastica and destroys the complex organization of the intima. Local metabolic derangements result in the local production of cholesterol within branching, stellate cells, which he suggests may be a type of vascular-nerve cell. Calcium and hyaline are locally produced simultaneously as a result of deranged metabolism. This idea of local production of cholesterol within cells is closely allied to Thannhauser's view (H62) regarding the development of primary xanthoma due to local cell overproduction.

If cholesterol enters the arterial wall by some method other than diffuse infiltration, other explanations of its entrance and its localization must be put

<sup>3</sup> We too have seen 3 types of "early" lesions in the chick: (1) foam cells, (2) mucoid degeneration and extracellular lipid and (3) fibrosis.

forward. Another theory has been advanced by Leary (D41) who has observed foam cells in the earliest human microscopic lesions, i.e., intracellular cholesterol in the earliest lesion rather than extracellular lipid as would appear from primary infiltration, and rather than preliminary mucoid degeneration as would appear from primary injury.

Further evidence against the theory of infiltration or imbibition has been gathered by Winternitz and his associates (G9, G10). Their studies of the arterial blood supply have disclosed an intramural intimal circulation anastomosing with the adventitial vasa (G9). These intimal vasa are most numerous at the origins of branching arteries and generally increase in number with age. Intimal vasa are always found in association with intimal atherosclerotic lesions (G10) so that the association has seemed more than fortuitous. These investigators have observed frequent intramural hemorrhages from these vasa and have advanced the hypothesis that such hemorrhages with the disintegration of red blood corpuscles and liberation of their contained lipids and cholesterol serve as the starting point for atherosclerosis (G9, G10).

Our own observations have led us to a hypothesis which combines some of the evidence of Leary and Winternitz with our own. Our observation of clusters of foam cells within intimal vasa (D16) has indicated to us the importance of both the intimal blood supply and the importance of cholesterol-bearing foam cells. The localization of foam cells is determined by the presence of intimal vasa, their number and distribution. In the coronary arteries where developmental intimal thickening has occurred, intimal vasa have been observed by Leary (D39) and others. At points of branching the presence of intimal vasa (G10) permits the development of lesions. Any vascularized scar of the arterial wall caused by arteritis (syphilitic, rheumatic, etc.) would provide the vasa for localization of lesions; while an old avascular scar would tend to remain free of atheroma. This indicates that not only the blood supply but the simultaneous presence of cholesterol-bearing foam cells is necessary for lesions to occur. This could account for the formation of atheroma around the edges of arterial scars with fibrous centers (D72, C18). The origin of the foam cells in experimental cholesterol atherosclerosis appears to be in the reticulo-endothelial cells of the liver (D16) and perhaps other organs (D41). Their origin in man remains to be determined.

7. *The Rôle of Tension and Strain:* Increased arterial pressure may accelerate intimal thickening and may affect the vascularity in its favored locations and thus may hasten the occurrence of atheroma. This may account for the greater frequency of atherosclerosis in hypertensive patients, as well as the more common presence of pulmonary atherosclerosis in pulmonary hypertension (G6). In the rabbit, as well as man, this correlation with systemic hypertension has been found (C6, C44).

The same mechanism operates in all likelihood in causing intimal fibrosis to occur in regions of branching since it is here that the constant impingement of the flowing blood stream exerts its greatest strain. Similar processes can be expected to occur wherever the stream becomes turbulent and eddies are set up.

In addition regions near eddies are places into which foam cells may be sifted by hydraulic forces and so can more readily plug up vasa.

#### SUMMARY

The experimental and clinical evidence has been assayed and the various concepts of atherosclerosis critically reviewed.

We may summarize our conclusions as to the interplay of forces resulting in the clinical disease atherosclerosis as follows: Cholesterol plays a key rôle and is an essential substance in the development of atheroma. Furthermore, the thyroid hormone and thyroid-stimulating-hormone affect the rate of transport and storage of cholesterol, thereby playing an essential part in the genesis of atherosclerosis. The localization of lesions is influenced by the process of physiological maturation and differentiation of the intima which goes on up to the age of 30, particularly in the epicardial portion of the coronary arteries, and in the aorta generally but more marked at certain sites. The development of vasa vasorum in the intima with openings in the arterial lumen likewise determines the localization of lesions. When hypertension occurs, on whatever basis, its presence hastens and augments the development of atheroma. But hypertension alone, without the action of the cholesterol factor, will not produce atheroma. Syphilis, rheumatic arteritis and other inflammatory arterial diseases may augment atherosclerosis by the augmentation of both the local tissue factors mentioned, namely intimal thickening, and the number of vasa vasorum.

Tremendous gaps in our knowledge make it impossible to set up a fully substantiated theory, but a working hypothesis has been advanced and some of the aspects of the problem requiring study have been suggested.

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#### BIBLIOGRAPHY

##### A. INCIDENCE OF ARTERIOSCLEROSIS, MORBIDITY AND MORTALITY, AGE GROUPS AFFECTED, SEX, ETC.

##### *I. Human*

- A1. ASCHOFF, L.: Lectures on Pathology, Ch. VI, Atherosclerosis, p. 131-154, New York, Paul B. Hoeber, 1924.
- A2. BOWEN, B. D., REGAN, J. S. AND KOENIG, E. C.: Development of Arteriosclerosis in the Diabetic. *Ann. Int. Med.* 12: 1996, 1939.
- A3. Bureau of the Census: Mortality Summary, Vital Statistics—Special Reports, Washington, Volume 16, 1940.
- A4. Bureau of the Census: Vital Statistics—Special Reports, Washington, Volume 17, 1941.
- A5. DRY, J. J. AND HINES, E. A.: The Rôle of Diabetes in the Development of Degenerative Vascular Disease: With Special Reference to the Incidence of Retinitis and Peripheral Neuritis. *Ann. Int. Med.* 14: 1893, 1941.
- A6. FRENCH, A. J. AND DOCK, W.: Fatal Coronary Arteriosclerosis in Young Soldiers. *J. A. M. A.* 124: 1233, 1944.

- A7. GLENDY, R. E., LEVINE, S. A. AND WHITE, P. D.: Coronary Disease in Youth. *J. A. M. A.* 109: 1775, 1937.
- A8. GROEDEL, F. M.: Observations on Circulatory System of Combatants During World War I. *Exper. Med. & Surg.* 1: 94, 1943.
- A9. HIRSCH, S.: Atheroma in Children. *Cardiologia*, 5: 122, 1941.
- A10. JOSLIN, E. P.: Arteriosclerosis in Diabetes. *Ann. Int. Med.* 4: 54, 1930.
- A11. MASTER, A. M., DACK, S. AND JAFFE, H. L.: Age, Sex and Hypertension in Myocardial Infarction Due to Coronary Occlusion. *Arch. Int. Med.* 64: 767, 1939.
- A12. MUKHERJEE, A. B. AND TRIBEDI, B. P.: Atheromatous Lesions in Bengal. Observations on 4000 Unselected Autopsies. *J. Indiana Med. A.* 12: 285, 1943.
- A13. ROOT, H. F., BLAND, E. F., GORDON, W. H. AND WHITE, P. D. Coronary Atherosclerosis in Diabetes Mellitus; A Postmortem Study. *J. A. M. A.* 113: 27, 1939.
- A14. SYDENSTRICKER, E.: Chap. 5, Statistical Study of Arteriosclerosis. In COWDRY, E. V., *Arteriosclerosis—A Survey of the Problem*. New York, The MacMillan Company, 1933.
- A15. WALSH, B. J., BLAND, E. F., TAQUINI, A. C. AND WHITE, P. D.: Association of Gall Bladder Disease and of Peptic Ulcer with Coronary Disease; Postmortem Study. *Am. Heart J.* 21: 689, 1941.
- A16. WARREN, S.: *The Pathology of Diabetes Mellitus*. Philadelphia, Lea & Febiger, 1938.

## II. Animal

- A17. DAUBER, D. V.: Spontaneous Atherosclerosis in Chickens. *Arch. Path.* 38: 46, 1944.
- A18. FOX, H.: Chap. 6, Arteriosclerosis in Lower Mammals and Birds: Its Relation to the Disease in Man. In COWDRY, E. V., *Arteriosclerosis—A Survey of the Problem*. New York, The MacMillan Company, 1933.
- A19. FOX, H.: Some Comments on Arteriosclerosis in Wild Mammals and Birds. *Bull. New York Acad. Med.* 15: 748, 1939.
- A20. HUEPER, W. C.: Spontaneous Arteriosclerosis in Rats. *Arch. Path.* 20: 708, 1935.
- A21. HUEPER, W. C.: Cartilaginous Foci in Hearts of White Mice and Rats. *Arch. Path.* 27: 466, 1939.
- A22. HUMMEL, K. P. AND BARNES, L. L.: Calcification of the Aorta, Heart and Kidneys of the Albino Rat. *Am. J. Path.* 14: 121, 1938.
- A23. NUZUM, F. R., ELLIOTT, A. H., EVANS, R. D. AND PRIEST, B. V.: The Occurrence and Nature of Spontaneous Arteriosclerosis and Nephritis in the Rabbit. *Arch. Path.* 10: 697, 1930.
- A24. WILENS, S. L. AND SPROUL, E. E.: Spontaneous Cardiovascular Disease in the Rat. I. Lesions of the Heart. *Am. J. Path.* 14: 177, 1938.
- A25. WILENS, S. L. AND SPROUL, E. E.: Spontaneous Cardiovascular Disease in the Rat. II. Lesions of the Vascular System. *Am. J. Path.* 14: 201, 1938.

## B. HISTORICAL: FIRST KNOWLEDGE OF INCIDENCE, DEVELOPMENT OF KNOWLEDGE WITH GROWTH OF SCIENCE OF PATHOLOGY

- B1. LONG, E. R.: Chap. 1, The Development of our Knowledge of Arteriosclerosis. In COWDRY, E. V., *Arteriosclerosis—A Survey of the Problem*. New York, The MacMillan Company, 1933.

## C. EXPERIMENTAL: MECHANICAL, TOXIC AND INFECTIOUS APPROACHES

- C1. ADLER, I.: Further Studies in Experimental Atherosclerosis. *J. Exper. Med.* 26: 581, 1917.
- C2. ANITSCHKOW, N.: Chap. 10, Experimental Arteriosclerosis in Animals. In COWDRY, E. V., *Arteriosclerosis—A Survey of the Problem*. New York, The MacMillan Company, 1933.



- C3. BALO, J.: Die mit Ammonium-hydroxydvergiftung erzeugbare experimentelle Arteriosklerose. *Frankfurt. Ztschr. f. Path.* 52: 205, 1938.
- C4. BLASON, R. L., SMITH, K. G. AND SEMENOV, H.: Experimental Arteritis and Arteriosclerosis Associated with Streptococcal Inoculation. *Arch. Path.* 12: 924, 1931.
- C5. CHRISTIANSON, O. O.: Lesions Produced in Dogs by Injection of Lipids: Human Fat, Fatty Acids, Soaps, Cholesterol. *Arch. Path.* 27: 1011, 1939.
- C6. DILL, L. V. AND ISENHOUR, C. E.: Occurrence of Atheroma in Rabbits with Renal Hypertension. *Arch. Path.* 33: 655, 1942.
- C7. DOMINGUEZ, R.: Note on Arteriosclerosis in Rabbits Caused by Some Samples of Uranium Nitrite. *Science*, 64: 407, 1926.
- C8. DOMINGUEZ, R.: Experimental Atherosclerosis and Blood Pressure in the Rabbit. *J. Exper. Med.* 46: 463, 1927.
- C9. DOMINGUEZ, R.: Effect on the Blood Pressure of the Rabbit of Arteriosclerosis and Nephritis Caused by Uranium. *Arch. Path.* 5: 577, 1928.
- C10. DUFF, G. L., HAMILTON, J. D. AND MAGNER, D.: Experimental Production of Arteriolonecrosis and Medionecrosis of Arteries by Means of Tyramine Injections. *Proc. Soc. Exper. Biol. & Med.* 41: 295, 1939.
- C11. FOX, R. A. AND JONES, L. R.: Vascular Pathology in Rabbits Following Administration of Foreign Protein. *Proc. Soc. Exper. Biol. & Med.* 55: 294, 1944.
- C12. GOLDBERG, S. A. AND SIMPSON, S.: Certain Pathological Tissue Changes in Thyroidectomized Sheep. *Proc. Soc. Exper. Biol. & Med.* 21: 567, 1924.
- C13. GOORMAGHTIGH, N. AND HANDOVSKY, H.: Vitamin D, thyroïde et pathologie vasculaire. *Bull. de l'académie Royale de Méd. de Belgique*, 6: 132, 1938.
- C14. GOORMAGHTIGH, N. AND HANDOVSKY, H.: Effect of Vitamin D<sub>2</sub> (Calciferol) on the Dog. *Arch. Path.* 26: 1144, 1938.
- C15. HALL, G. E.: Experimental Heart Disease. *Ann. Int. Med.* 12: 907, 1939.
- C16. HAM, A. W.: Mechanism of Calcification in Heart and Aorta in Hypervitaminosis D. *Arch. Path.* 14: 613, 1932.
- C17. HAM, A. W. AND LEWIS, M. D.: Experimental Intimal Sclerosis of the Coronary Arteries of Rats. *Arch. Path.* 17: 356, 1934.
- C18. HARRISON, C. V.: Experimental Arterial Disease Produced by Cholesterol and Vitamin D. *J. Path. & Bact.* 36: 447, 1933.
- C19. HEINLEIN, H.: Organveränderungen durch körpereigene kreislaufwirksame Stoffe; Acetylcholin. *Ztschr. f. d. ges. exper. Med.* 105: 406, 1939.
- C20. HOLMAN, R. L. AND HEWITT, W. C.: Experimental Necrotizing Arteritis. II. Mercuric Chloride as Effective as Uranium Nitrite in its Production. *Proc. Soc. Exper. Biol. & Med.* 49: 58, 1942.
- C21. HUEPER, W. C.: Experimental Studies in Cardiovascular Pathology. III. Polyvinyl Alcohol Atheromatosis in Arteries of Dogs. *Arch. Path.* 31: 11, 1941.
- C22. HUEPER, W. C.: Experimental Studies in Cardiovascular Pathology. IV. Methyl Cellulose Atheromatosis and Thesaurosis. *Arch. Path.* 33: 1, 1942.
- C23. HUEPER, W. C.: Macromolecular Substances as Pathogenic Agents. *Arch. Path.* 33: 267, 1942.
- C24. Hueper, W. C.: Experimental Studies in Cardiovascular Pathology. VI. Pectin Atheromatosis and Thesaurosis in Rabbits and in Dogs. *Arch. Path.* 34: 883, 1942.
- C25. HUEPER, W. C.: Experimental Studies in Cardiovascular Pathology. V. Effects of Intravenous Injections of Gum Arabic, Egg Albumin and Gelatin upon the Blood and Organs of Dogs and Rabbits. *Am. J. Path.* 18: 895, 1942.
- C26. HUEPER, W. C. AND ICHNIOWSKI, C. T.: Experimental Studies in Cardiovascular Pathology. VIII. Late Vascular Reactions of Histamine Shock in Dogs. *Am. J. Path.* 20: 211, 1944.

- C27. HUEPER, W. C. AND LANDSBERG, J. W.: Experimental Studies in Cardiovascular Pathology. I. Pathologic Changes in the Organs of Rats Produced by Chronic Nitrite Poisoning. *Arch. Path.* 29: 633, 1940.
- C28. HUEPER, W. C. AND MARTIN, G. J.: Tyrosine Poisoning in Rats. *Arch. Path.* 35: 685, 1943.
- C29. JOBLING, J. W. AND MEEKER, D. R.: Further Investigations on Experimental Atherosclerosis. *Arch. Path.* 22: 293, 1936.
- C30. MACCALLUM, W. G.: Chap. 12, Acute and Chronic Infections as Etiological Factors. In COWDRY, E. V., *Arteriosclerosis—A Survey of the Problem*. New York, The MacMillan Company, 1933.
- C31. MELLON, R. R., BAKER, M. R., AND MCILROY, A. P.: Experimental Necrotizing Arteriolitis Induced by a Protein Cleavage Product. *Proc. Soc. Exper. Biol. & Med.* 33: 92, 1935.
- C32. MENTEN, M. L. AND KING, C. G.: Influence of Vitamin C Level on Resistance to Diphtheria Toxin. II. Production of Diffuse Hyperplastic Arteriosclerosis and Degeneration in Various Organs. *J. Nutrition*, 10: 141, 1935.
- C33. OPPER, L.: Experimental Vascular Disease in Rats Produced by Multiple Depletions of Vitamin A. *Proc. Soc. Exper. Biol. & Med.* 40: 449, 1939.
- C34. RAAB, W.: Arterioskleroseentstehung und Nebennieren—lipoid—adrenalin-("NLA")-Komplex. *Ztschr. f. d. ges. exper. Med.* 105: 657, 1939.
- C35. RAMSEY, E. M. AND ALPERT, L. K.: Response of Tissue of the Intima to Injurious Agents. *Proc. Soc. Exper. Biol. & Med.* 30: 1433, 1933.
- C36. RAMSEY, E. M., GAISER, D. W., CARDEN, G. A. JR., Lecompte, P. AND TENNANT, R.: Studies in the Pathology of Vascular Disease. I. Nutrition of the Blood Vessel Wall: Review of the Literature. *Yale J. Biol. & Med.* 9: 13, 1936.
- C37. RICH, A. R. AND DUFF, G. L.: The Production of Hyaline Arteriolosclerosis and Arteriolonecrosis by Means of Proteolytic Enzymes. *Bull. Johns Hopkins Hosp.* 61: 63, 1937.
- C38. RICH, A. R. AND GREGORY, J. E.: The Experimental Demonstration that Periarteritis Nodosa is a Manifestation of Hypersensitivity. *Bull. Johns Hopkins Hosp.* 72: 65, 1943.
- C39. RICH, A. R. AND GREGORY, J. E.: Experimental Evidence that Lesions with the Basic Characteristics of Rheumatic Carditis can Result from Anaphylactic Hypersensitivity. *Bull. Johns Hopkins Hosp.* 73: 239, 1943.
- C40. SHEEHAN, J. F.: Foam Cell Plaques in the Intima of Irradiated Small Arteries (One Hundred to Five Hundred Microns in External Diameter). *Arch. Path.* 37: 297, 1944.
- C41. SHORT, J. J., BRUGER, M. AND JAFFE, L.: Production of Intimal Changes in the Arteries Attempted in the Rat by Prolonged Feeding of Aceto-Acetic Acid. *Arch. Path.* 22: 543, 1936.
- C42. SPIES, T. D.: Production of Nonfatal Vascular Sclerosis in Rabbits by Means of Viosterol (Irradiated Ergosterol). *Arch. Int. Med.* 50: 443, 1932.
- C43. Vanderveer, H. L.: Hypervitaminosis D<sup>a</sup> and Arteriosclerosis. *Arch. Path.* 12: 941, 1931.
- C44. WILENS, S. L.: The Effect of Postural Hypertension on the Development of Atheromatosis in Rabbits Fed Cholesterol. *Am. J. Path.* 19: 293, 1943.

#### D. EXPERIMENTAL CHOLESTEROL ATHEROMATOSIS

Nature (Pathology), Chemistry, Occurrence in Different Species, Effect of Various Factors on (Sex Hormones, Thyroid, Lipotropic Substances, etc.) Pathogenesis, Relationship to Human Lesions, etc.

- D1. ADLER, I.: Further Studies in Experimental Atherosclerosis. *J. Exper. Med.* 26: 581, 1917.

- D2. ANITSCHKOW, N.: Chap. 10, Experimental Arteriosclerosis in Animals. In COWDRY, E. V., *Arteriosclerosis—A Survey of the Problem*. New York, the MacMillan Company, 1933.
- D3. BAILEY, C. H.: Cholesterol Atheroma in Rabbits. *Proc. Soc. Exper. Biol. & Med.* 12: 69, 1915.
- D4. BAILEY, C. H.: Atheroma and Other Lesions Produced in Rabbits by Cholesterol Feeding. *J. Exper. Med.* 23: 69, 1916.
- D5. BAILEY, C. H.: Observations on Cholesterol-Fed Guinea Pigs. *Proc. Soc. Exper. Biol. & Med.* 13: 60, 1916.
- D6. BAUMANN, C. A. AND RUSCH, W. P.: Effect of Choline on Atherosclerosis in the Rabbit Aorta. *Proc. Soc. Exper. Biol. & Med.* 38: 647, 1938.
- D7. BLAISDELL, F. E. AND CHANDLER, L. R.: The Relation Between Cholesterolemia and Deposits of Cholesterol in the Gall Bladder: An Experimental Study. *Am. J. M. Sc.* 174: 492, 1927.
- D8. BOLLMANN, J. L. AND FLOCK, E. V.: Phospholipid Changes in Experimental Cholesterol Arteriosclerosis. *Am. Soc. Path. Meetings* 17: 439, 1941.
- D9. BRUGER, M. AND FITZ, F.: Effect of Prolonged Administration of Thyrotropic Factor of the Anterior Lobe of the Pituitary on Experimental Atheromatosis in Rabbits. *Arch. Path.* 25: 637, 1938.
- D10. BRUGER, M., WRIGHT, I. S. AND WILAND, J.: Experimental Atherosclerosis. V. Effect of Testosterone Propionate and Estradiol Dipropionate on the Cholesterol Content of the Blood and the Aorta in Castrate Female Rabbits. *Arch. Path.* 36: 612, 1943.
- D11. CHRISTIANSON, O. O.: Lesions Produced in Dogs by Injection of Lipids: Human Fat, Fatty Acids, Soaps, Cholesterol. *Arch. Path.* 27: 1011, 1939.
- D12. CLARKSON, S. AND NEWBURGH, L. H.: Relation Between Atherosclerosis and Ingested Cholesterol in Rabbit. *J. Exper. Med.* 43: 595, 1926.
- D13. COLE, W. H., CLARK, H. AND WOMACK, N. A.: Preparation of a Cholesterol Emulsion for Experimental Intravenous Administration. *J. Lab. & Clin. Med.* 26: 1679, 1941.
- D14. COOK, R. P. AND McCULLAGH, G. P.: A Comparative Study of Cholesterol Metabolism and Its Relation to Fatty Infiltration with Particular Reference to Experimental Cholesterol Atheroma. *Quart. J. Exper. Physiol.* 29: 283, 1939.
- D15. DAUBER, D. V. AND KATZ, L. N.: Experimental Cholesterol Atheromatosis in an Omnivorous Animal, the Chick. *Arch. Path.* 34: 937, 1942.
- D16. DAUBER, D. V. AND KATZ, L. N.: Experimental Atherosclerosis in the Chick. *Arch. Path.* 36: 473, 1943.
- D17. DOMINGUEZ, R.: Experimental Atherosclerosis and Blood Pressure in the Rabbit. *J. Exper. Med.* 46: 463, 1927.
- D18. DRAGSTEDT, L. R., CLARK, D. E., JULIAN, O. E., VERMEULEN, C. AND GOODPASTURE W. C.: Arteriosclerosis in Pancreatic Diabetes. *Surgery*, 8: 353, 1940.
- D19. DRAGSTEDT, L. R., PROHASKA, VAN J., CLARK, D. E. AND JULIAN, O. C.: The Effect of Lipocain on Cholesterol Arteriosclerosis in Rabbits. *Am. J. Physiol.* 129: 348, 1940.
- D20. DUFF, G. L.: Experimental Cholesterol Arteriosclerosis and its Relationship to Human Arteriosclerosis. *Arch. Path.* 20: 81 and 259, 1935.
- D21. DUFF, G. L.: The Nature of Experimental Cholesterol Arteriosclerosis in the Rabbit. *Arch. Path.* 22: 161, 1936.
- D22. EBERHARD, T. P.: Effect of Alcohol on Cholesterol Induced Atherosclerosis in Rabbits. *Arch. Path.* 21: 616, 1936.
- D23. FLEISCHMANN, W. AND FRIED, I. A.: Studies on the Hypercholesterolemia of Immature Fowl Induced by Estrogens. *Fed. Proc.* 3: 10, 1944.
- D24. FLEXNER, J., BRUGER, M. AND WRIGHT, I. S.: II. Effect of Thiamin Hydrochloride and Ascorbic Acid on Experimental Atherosclerosis in Rabbits. *Arch. Path.* 31: 82, 1941.

- D25. FORBES, J. C.: Effect of Thyroxine on Neutral Fat and Cholesterol Content of the Body and Liver of Rats. *Endocrinology*, 35: 126, 1944.
- D26. FRIEDLAND, I. B.: Untersuchungen über den Einfluss der Schilddrüsenpräparate auf die experimentelle Hypercholesterinämie und Atherosklerose. *Zeitschr. f. d. ges. exper. Med.* 87: 683, 1933.
- D27. HAM, A. W. AND LEWIS, M. D.: Experimental Intimal Sclerosis of the Coronary Arteries of Rats. *Arch. Path.* 17: 356, 1934.
- D28. HIMSWORTH, H. P.: Effect of Choline on Cholesterol Atheromatosis in Rabbits. *Acta. Med. Skandinav. Suppl.* 90: 158, 1938.
- D29. HIRSCH, E. F. AND WEINHOUSE, S.: The Rôle of the Lipids in Atherosclerosis. *Physiol. Rev.* 23: 185, 1943.
- D30. HUBER, M. J., BROUN, G. O. AND CASEY, A. E.: Prevention of Cholesterol Arteriosclerosis in the Rabbit by Use of Pancreatic Extract (Lipocaic). *Proc. Soc. Exper. Biol. & Med.* 37: 441, 1937.
- D31. HURWITZ, M. AND FRIEDBERG, L.: Relationship of Heart Size to Cholesterol Content in Experimental Atheromatosis in the Rabbit. *Arch. Path.* 34: 875, 1942.
- D32. JOBLING, J. W. AND MEEKER, D. R.: Further Investigations on Experimental Atherosclerosis. *Arch. Path.* 72: 293, 1936.
- D33. KAWAMURA, R.: Neue Beiträge zur Morphologie und Physiologie der Cholesterinsteatose. *Jena, Gustav Fischer*, 1927.
- D34. KAWAMURA, R. AND NAKANOIN, T.: Cholesterinesorption und Cholesteatose des Darmes. *Verhandl. Jap. path. Gesell.* 6: 93, 1916.
- D35. KATZ, L. N., SANDERS, A., MEGIBOW, R. S. AND CARLEN, S.: Heart Size and Experimental Atheromatosis in the Rabbit. *Am. J. M. Sc.* 200: 731, 1940.
- D36. KESTEN, H. D., MEEKER, D. R. AND JOBLING, J. W.: Attempt to Produce Atherosclerosis in Chickens by Feeding Cholesterol. *Proc. Soc. Exper. Biol. & Med.* 34: 818, 1936.
- D37. KESTEN, H. D. AND SILBOWITZ, R.: Experimental Atherosclerosis and Soya Lecithin. *Proc. Soc. Exper. Biol. & Med.* 49: 71, 1942.
- D38. KLOTZ, O. AND BOTHWELL, M. E.: Experimental Calcification. *Proc. Soc. Exper. Biol. & Med.* 12: 159, 1915.
- D39. LEARY, T.: Experimental Atherosclerosis in the Rabbit Compared with Human (Coronary) Atherosclerosis. *Arch. Path.* 17: 453, 1934.
- D40. LEARY, T.: Atherosclerosis; Etiology. *Arch. Path.* 21: 459, 1936.
- D41. LEARY, T.: The Genesis of Atherosclerosis. *Arch. Path.* 32: 507, 1941.
- D42. LIEBIG, H.: Die Beeinflussung der experimentellen Atherosklerose durch Jodbehandlung. *Arch. f. exp. Path. u. Pharmakol.* 159: 265, 1931.
- D43. LÖWENTHAL, K.: Experimentelle Atherosklerose bei Omnivoren. *Frankfurt. Zeitschr. f. Path.* 34: 145, 1926.
- D44. LÖWENTHAL, K.: Experimentelle Atherosklerose. *Med. Klin.* 22: 770, 1926.
- D45. LUDDEN, J. B., BRUGER, M. AND WRIGHT, I. S.: Experimental Atherosclerosis. IV. Effect of Testosterone Propionate and Estradiol Dipropionate on Experimental Atherosclerosis in Rabbits. *Arch. Path.* 33: 58, 1942.
- D46. MALISOFF, W. M.: Prevention of Atherosclerosis in Rabbits. I. Administration of Potassium Thiocyanate. *Proc. Soc. Exper. Biol. & Med.* 35: 356, 1936.
- D47. MANCKE, R.: Über sklerotische Organveränderungen insonderheit der Arterien; III. Mitteilung. Untersuchungen über experimentelle Veränderungen der Arterien durch Produkte des Kohlehydratstoffwechsels. *Arch. f. exper. Path. u. Pharmakol.* 141: 228, 1929.
- D48. MEEKER, D. R. AND KESTEN, H. D.: Experimental Atherosclerosis and High Protein Diets. *Proc. Soc. Exper. Biol. & Med.* 45: 543, 1940.
- D49. MEEKER, D. R. AND KESTEN, H. D.: Effect of High Protein Diets on Experimental Atherosclerosis of Rabbits. *Arch. Path.* 31: 147, 1941.
- D50. MEEKER, D. R., KESTEN, H. D. AND JOBLING, J. W.: Effect of Iodine on Cholesterol-Induced Atherosclerosis. *Arch. Path.* 20: 337, 1935.

- D51. MOEHLIG, R. C.: The Rôle of the Posterior Pituitary Gland in the Experimental Production of Arteriosclerosis. *Endocrinology*, 14: 337, 1930.
- D52. MOEHLIG, R. C. AND OSIUS, E. A.: The Pituitary Factor in Arteriosclerosis. Its Experimental Production in Rabbits. *Ann. Int. Med.* 4: 578, 1930.
- D53. MURADA, K. AND KATSAKA, B.: Alimentary Atherosclerosis in Castrated Animals (Rabbits). *Jap. Med. Lit.* 6: 13, 1921.
- D54. MURATA, M. AND KATAOKA, S.: Experimentelle Arteriosklerose und Schilddrüsenfütterung. *Trans. Japan. Path. Soc.* 8: 221, 1918.
- D55. PAGE, I. H. AND BERNHARD, W. G.: Cholesterol Induced Atherosclerosis. Its Prevention in Rabbits by the Feeding of an Organic Iodine Compound. *Arch. Path.* 19: 530, 1935.
- D56. RAWSON, R. W., HERTZ, S. AND MEANS, J. H.: Thiocyanate Goiter in Man. *Ann. Int. Med.* 19: 829, 1943.
- D57. SEEL, H. AND CREUZBERG, G.: Experimentelle und Klinische Beiträge zur Pharmakologie des Jods. I. Mitteilung: Über die Wirkung des Jods auf die Cholesterin und die Ergosterinsklerose. *Arch. für exper. Path. und Pharmakol.* 161: 674, 1931.
- D58. SHAPIRO, S.: Influence of Thyroidectomy, Splenectomy, Gonadectomy and Suprarenalectomy Upon the Development of Experimental Atherosclerosis in the Rabbit. *J. Exper. Med.* 45: 595, 1927.
- D59. STEINER, A.: Effect of Choline on the Production of Experimental Atherosclerosis in Rabbits. *Proc. Soc. Exper. Biol. & Med.* 38: 231, 1938.
- D60. STEINER, A.: Action of Choline on Experimental Aortic Atherosclerosis. *Proc. Soc. Exper. Biol. & Med.* 39: 411, 1938.
- D61. TURNER, K. B.: Studies on the Prevention of Cholesterol Atherosclerosis in Rabbits. I. Effects of Whole Thyroid and of Potassium Iodide. *J. Exper. Med.* 58: 115, 1933.
- D62. TURNER, K. B. AND BIDWELL, E. H.: Further Observations on the Blood Cholesterol of Rabbits in Relation to Atherosclerosis. *J. Exper. Med.* 62: 721, 1935.
- D63. TURNER, K. B. AND BIDWELL, E. H.: Some Effects of Iodine Given to Rabbits after a Period of Cholesterol Feeding. *Proc. Soc. Exper. Biol. & Med.* 35: 656, 1937.
- D64. TURNER, K. B. AND DELAMATAR, A.: Effect of Thyrotropic Hormone on Blood Cholesterol of Thyroidectomized Rabbits. *Proc. Soc. Exper. Biol. & Med.* 49: 150, 1942.
- D65. TURNER, K. B. AND KHAYAT, G. B.: Studies on the Prevention of Cholesterol Atherosclerosis in Rabbits. II. Influence of Thyroidectomy Upon the Protective Action of Potassium Iodide. *J. Exper. Med.* 58: 127, 1933.
- D66. TURNER, K. B., PRESENT, C. H. AND BIDWELL, E. K.: The Rôle of the Thyroid in the Regulation of the Blood Cholesterol of Rabbits. *J. Exper. Med.* 67: 111, 1938.
- D67. UCHIYAMA, T.: Beiträge zur Morphologie des Lipoidstoffwechsels. IV. Über die Steatosen des Arteriellen Gefäßsystems unter normalen und abnormen Fütterungsbedingungen (cholesterinölfütterung) nebst Bemerkungen über die Befunde an anderen Organsystemen. *Virch. Arch. f. path. Anat.* 277: 642, 1930.
- D68. VERMEULEN, C. W., ALLEN, J. G., CLARK, D. E., JULIAN, O. C. AND DRAGSTEDT, L. R.: The Effect of Lipocae and Cholesterol Administration in Rabbits. *Am. J. Physiol.* 133: 476, 1941.
- D69. VERMEULEN, C. W., DRAGSTEDT, L. R., CLARK, D. E., JULIAN, O. E. AND ALLEN, J. G.: Effect of the Administration of Lipocae and Cholesterol in Rabbits. *Arch. Surg.* 44: 260, 1942.
- D70. WEINHOUSE, S.: The Blood Cholesterol. *Arch. Path.* 35: 438, 1943.
- D71. WEINHOUSE, S. AND E. F. HIRSCH.: II. Tissues in Experimental Atherosclerosis of Rabbits. *Arch. Path.* 30: 856, 1940.
- D72. WILENS, S. L.: The Distribution of Intimal Atheromatous Lesions in the Arteries of Rabbits on High Cholesterol Diets. *Am. J. Path.* 18: 63, 1942.



- D73. WOLKOFF, K.: Zur Frage der Morphologie der Lipoid Ablagerungen im Organismus der Téprrmause bei Verschiedener Nahrungsart. *Ztschr. f. Krebsforsch.* 31: 291, 1930.
- D74. YUASA, D.: Über die experimentelle Cholesterinkrankheit bei Omnivoren. *Beitr. z. path. anat. u. z. allg. Path.* 80: 570, 1928.
- D75. YAMAGUCHI, M.: Cholesterol Metabolism in Organisms. First Report: The Cholesterol Problem in Regard to Birds. *Jap. J. M. Sc. Abs.* 2: 143, 1925.

#### E. THE RÔLE OF LOCAL TISSUE FACTORS IN EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS AND HUMAN ATHEROSCLEROSIS

- E1. DILL, L. V. AND ISENHOUR, C. E.: The Occurrence of Atheroma in the Aorta in Rabbits with Renal Hypertension. *Arch. Path.* 33: 655, 1942.
- E2. DOMINGUEZ, R.: Experimental Atherosclerosis and Blood Pressure in the Rabbit. *J. Exper. Med.* 46: 463, 1927.
- E3. FROTHINGHAM, C. JR.: Relation Between Acute Infectious Diseases and Arterial Lesions. *Arch. Int. Med.* 8: 153, 1911.
- E4. GLASER, F.: Vegetatives Nervensystem, Hypercholesterinämie, und Arteriosklerose in ihren Beziehungen zu einander. *Klin. Wchnschr.* 6: 2377, 1927.
- E5. HARRISON, C. V.: Experimental Arterial Disease Produced by Cholesterol and Vitamin D. *J. Path. & Bact.* 36: 447, 1933.
- E6. HARRISON, C. V.: The Effect of Sympathectomy on the Development of Experimental Arterial Disease. *J. Path. & Bact.* 48: 353, 1939.
- E7. HIRSCH, S.: L'athérome aortique des enfants. Etudes a propos des débuts de la Soi-disant artériosclérose. *Cardiologia*, 5: 122, 1941.
- E8. KRAFKA, J. JR.: The Mechanical Factors in Arteriosclerosis. *Arch. Path.* 23: 1, 1937.
- E9. LEARY, T.: Pathology of Coronary Sclerosis. *Am. Heart J.* 10: 328, 1935.
- E10. LEARY, T.: Arteriosclerosis. *Bull. New York Acad. Med.* 17: 887, 1941.
- E11. RAMSEY, E. M., GAISER, D. W., CARDEN, G. A. JR. AND TENNANT, R.: Studies in the Pathology of Vascular Diseases. I. Nutrition of the Blood Vessel Wall: Review of the Literature. *Yale J. Biol. & Med.* 9: 13, 1936.
- E12. SHEEHAN, J. F.: Foam Cell Plaques in the Intima of Irradiated Small Arteries (One Hundred to Five Hundred Microns in External Diameter). *Arch. Path.* 37: 297, 1944.
- E13. WILENS, S. L.: The Postmortem Elasticity of the Adult Human Aorta. Its Relation to Age and to the Distribution of Intimal Atheromas. *Am. J. Path.* 13: 811, 1936.
- E14. WILENS, S. L.: The Distribution of Intimal Atheromatous Lesions in the Arteries of Rabbits on High Cholesterol Diets. *Am. J. Path.* 18: 63, 1942.
- E15. WILENS, S. L.: The Effect of Postural Hypertension on the Development of Atheromatosis in Rabbits Fed Cholesterol. *Am. J. Path.* 19: 293, 1943.

#### F. CHOLESTEROL METABOLISM AND CLINICAL ATHEROSCLEROSIS

- F1. ASCHOFF, L.: Observations Concerning Relationship Between Cholesterol Metabolism and Vascular Disease. *Brit. Med. J.* 2: 1131, 1932.
- F2. BARKER, N. W.: Plasma Lipoids in Arteriosclerosis Obliterans. *Ann. Int. Med.* 13: 685, 1939.
- F3. BLUMENTHAL, H. T., LANSING, A. J. AND WHEELER, P. A.: Calcification of Media of Human Aorta and Its Relation to Intimal Arteriosclerosis. *Am. J. Path.* 20: 665, 1944.
- F4. BRUGER, M. AND CHASSIN, M. R.: The Cholesterol Content of the Thoracic Aorta and of the Renal Arteries in Human Necropsy Material: Correlation with Clinical Findings and Vascular Pathology. *J. Clin. Investigation* 19: 787, 1940.
- F5. BRUGER, M. AND ROSENKRANTZ, J. A.: Arteriosclerosis and Hypothyroidism. *J. Clin. Endocrinology*, 2: 176, 1942.

- F6. DAVIS, D., STERN, B. AND LESNICK, G.: The Lipid and Cholesterol Content of the Blood of Patients with Angina Pectoris and Arteriosclerosis. *Ann. Int. Med.* 11: 354, 1937.
- F7. ENGLEBERG, H. AND NEWMAN, B. A.: Xanthomatosis: A Cause of Coronary Artery Disease in Young Adults. *J. A. M. A.* 122: 1167, 1943.
- F8. GIBBS, C. B., BUCKNER, E. AND BLOOR, W. R.: Cholesterol to Cholesterol-ester Ratio in Plasma of Diabetics with Advanced Arteriosclerosis. *New England J. Med.* 209: 384, 1933.
- F9. HIRSCH, E. F. AND WEINHOUSE, S.: The Rôle of the Lipids in Atherosclerosis. *Physiol. Rev.* 23: 185, 1943.
- F10. HIRSCH, S.: L'athérome aortique des infants. Etudes a propos des débuts de la Soi-disant artériosclérose. *Cardiologia* 5: 122, 1941.
- F11. HUNT, H.: Cholesterol in Blood of Diabetics Treated at New England Deaconess Hospital. *New England J. Med.* 201: 659, 1929.
- F12. HURXTHAL, L. M. AND HUNT, H. M.: Clinical Relationships of Blood Cholesterol with a Summary of our Present Knowledge of Cholesterol Metabolism. *Ann. Int. Med.* 9: 717, 1935.
- F13. KÄRLSTROM, F.: Plasma Cholesterol, Electrocardiogram and Blood Pressure in Children with Diabetes Treated with a "Free Diet." *Acta Paediat.* 24: 177, 1939.
- F14. LANDÉ, K. AND SPERRY, W. M.: Human Atherosclerosis in Relation to the Cholesterol Content of the Blood Serum. *Arch. Path.* 22: 301, 1936.
- F15. LEARY, T.: Atherosclerosis, the Important Form of Arteriosclerosis; A Metabolic Disease. *J. A. M. A.* 105: 475, 1935.
- F16. LEARY, T.: Pathology of Coronary Sclerosis. *Am. Heart J.* 10: 328, 1935.
- F17. LEARY, T.: Atherosclerosis; Special Consideration of Aortic Lesions. *Arch. Path.* 21: 419, 1936.
- F18. LEARY, T.: Cholesterol Lysis in Atheroma. *Arch. Path.* 37: 16, 1944.
- F19. MCARTHUR, C. S.: The Acetone-Soluble Lipid of the Atheromatous Aorta. *Biochem. J.* 36: 559, 1942.
- F20. MEEKER, D. R. AND JOBLING, J. W.: A Chemical Study of Arteriosclerotic Lesions in the Human Aorta. *Arch. Path.* 18: 252, 1934.
- F21. MÜLLER, C.: Xanthomata, Hypercholesterinemia, Angina Pectoris. *Acta med. Scandinav. Suppl.* 89: 75, 1938.
- F22. RABINOWITCH, I. M.: Arteriosclerosis in Diabetes. I. Relationship Between Plasma Cholesterol and Arteriosclerosis. II. Effects of the High Carbohydrate-Low Calorie Diet. *Ann. Int. Med.* 8: 1436, 1935.
- F23. ROSENTHAL, S. R.: Studies in Atherosclerosis: Chemical, Experimental and Morphologic. I and II. Rôles of Cholesterol Metabolism, Blood Pressure and Structure of the Aorta; The Fat Angle of the Aorta (F.A.A.), and the Infiltration Expression Theory of Lipoid Deposit. *Arch. Path.* 18: 473, 660, and 827, 1934.
- F24. SCHÖNHEIMER, R.: Zur Chemie der gesunden und der atherosklerotischen Aorta. *Ztschr. f. physiol. Chem.* 160: 61, 1926.
- F25. SHAFFER, C. F.: Nutritional Rôle of Cholesterol in Human Coronary Arteriosclerosis. *Ann. Int. Med.* 20: 881, 1944.
- F26. SNAPPER, I.: Chinese Lessons to Western Medicine: A Contribution to Geographical Medicine from the Clinics of Peiping Union Medical College. New York, New York Interscience Publishers, Inc., 1941.
- F27. STEINER, A. AND DOMANSKI, B.: Serum Cholesterol Level in Coronary Arteriosclerosis. *Arch. Int. Med.* 71: 397, 1943.
- F28. THANNHAUSER, S. J. AND MAGENDANTZ, H.: The Different Clinical Groups of Xanthomatous Disease. *Ann. Int. Med.* 11: 1662, 1938.
- F29. WEINHOUSE, S.: The Blood Cholesterol. *Arch. Path.* 35: 438, 1943.

- F30. WEISS, S. AND MINOT, G. R.: Chap. 8, Nutrition in Relation to Arteriosclerosis. In COWDRY, E. V., *Arteriosclerosis—A Survey of the Problem*. New York, The MacMillan Company, 1933.
- F31. WHITE, P. AND HUNT, H.: Cholesterol of the Blood of Diabetic Children. *New England J. Med.* 202: 607, 1930.

## G. PATHOGENESIS OF ARTERIOSCLEROSIS IN LIGHT OF PRESENT KNOWLEDGE

- G1. DUFF, G. L.: Experimental Cholesterol Arteriosclerosis and its Relationship to Human Arteriosclerosis. *Arch. Path.* 20: 81 and 259, 1935.
- G2. HIRSCH, E. F. AND WEINHOUSE, S.: The Rôle of the Lipids in Atherosclerosis. *Physiol. Rev.* 23: 185, 1943.
- G3. HUEPER, W. C.: The Etiology and the Causative Mechanism of Arteriosclerosis and Atheromatosis. *Medicine*, 20: 397, 1941.
- G4. KRAFKA, J. JR.: The Mechanical Factors in Arteriosclerosis. *Arch. Path.* 23: 1, 1937.
- G5. LEARY, T.: Genesis of Atherosclerosis. *Arch. Path.* 32: 507, 1941.
- G6. MOSCHOWITZ, E.: The Cause of Arteriosclerosis. *Am. J. M. Sc.* 178: 244, 1929.
- G7. PAGE, I. H.: Some Aspects of the Nature of the Chemical Changes Occurring in Atheromatosis. *Ann. Int. Med.* 14: 1741, 1941.
- G8. ROSENTHAL, S. R.: Studies in Atherosclerosis: Chemical, Experimental and Morphologic. I. and II. Rôles of Cholesterol Metabolism, Blood Pressure and Structure of the Aorta; The Fat Angle of the Aorta (F.A.A.), and the Infiltration-Expression Theory of Lipoid Deposit. *Arch. Path.* 18: 473, 660 and 827, 1934.
- G9. WINTERNITZ, M. C., THOMAS, R. M. AND LeCOMPTE, P. M.: Studies in the Pathology of Vascular Disease. *Am. Heart J.* 14: 399, 1937.
- G10. WINTERNITZ, M. C., THOMAS, R. M. AND LeCOMPTE, P. M.: *The Biology of Arteriosclerosis*. Springfield, Ill., Charles C. Thomas, Publisher, 1938.

## H. CHOLESTEROL METABOLISM AND FACTORS AFFECTING IT

- H1. BARKER, M. H.: Pg. 316, Studies in Cholesterol Metabolism: Clinical and Experimental Observations. In *Medical Papers Dedicated to H. A. Christian*, Baltimore, Waverly Press, 1936.
- H2. BEST, C. H. AND RIDEOUT, J. H.: The Effect of Cholesterol and Choline on the Deposition of Liver Fat. *J. Physiol.* 78: 415, 1933.
- H3. BILLS, C. E.: Physiology of the Sterols, Including Vitamin D. *Physiol. Rev.* 15: 1, 1935.
- H4. BING, H. I., HECKSCHER, H. AND JESSEN, J.: Studies on the Fat Cholesterol Contents of the Blood in Rabbits Suffering from an Artificial Nephritis. *Acta path. et microbiol. Scandinav.* 2: 234, 1925.
- H5. BLOCH, K., BERG, B. N. AND RITTENBERG, D.: Biologic Conversion of Cholesterol to Cholic Acid. *J. Biol. Chem.* 149: 511, 1943.
- H6. BLOCH, K. AND RITTENBERG, D.: On the Utilization of Acetic Acid for Cholesterol Formation. *J. Biol. Chem.* 145: 625, 1942.
- H7. BLOOR, W. R.: *Fat Metabolism*, California, Stanford Univ. Press, 1932, vol. 1, p. 267.
- H8. BLOOR, W. R., OKEY, R. AND CORNER, G. W.: The Relation of the Lipids to Physiological Activity. *J. Biol. Chem.* 86: 291, 1930.
- H9. BRUGER, M.: Cholesteroluria in Bright's Disease. *Am. J. Clin. Path.* 5: 504, 1935.
- H10. BRUGER, M. AND SOMACH, J.: Diurnal Variations of the Cholesterol Content of the Blood. *J. Biol. Chem.* 97: 23, 1932.
- H11. BÜRGER, M.: Der Cholesterinhaushalt beim Menschen. *Ergeb. d. inn. Med. und Kinderh.* 34: 583, 1928.
- H12. COOK, R. P.: Cholesterol Feeding and Fat Metabolism. *Biochem. J.* 30: 1630, 1936.

- H13. COOK, R. P.: Fat Feeding and Cholesterol Absorption. *Biochem. J.* 31: 410, 1937.
- H14. COOK, R. P.: Cholesterol Metabolism. Acids Apparently Concerned in the Metabolism of Cholesterol. *Biochem. J.* 32: 1191, 1938.
- H15. CORCORAN, A. C. AND RABINOWITCH, I. M.: Study of the Blood Lipoids and Blood Protein in Canadian Eastern Arctic Eskimos. *Biochem. J.* 31: 343, 1937.
- H16. CORWIN, W.: Experimental Hypercholesteremia in Dogs. *Arch. Path.* 26: 456, 1938.
- H17. Current Comment. The Brain and Cholesterol Metabolism. *J. A. M. A.* 116: 2508, 1941.
- H18. DENIS, W.: Influence of Splenectomy on Metabolism in Anemia. *Arch. Int. Med.* 20: 79, 1917.
- H19. DEWEY, K.: Experimental Hypercholesterolemia. *Arch. Int. Med.* 17: 757, 1916.
- H20. DUNHAM, L. J. AND BRUNSCHWIG, A.: Intravenous Administration of Fat for Nutritional Purposes. *Arch Surg.* 48: 395, 1944.
- H21. ENTENMAN, C. E. AND CHAIKOFF, I. L.: The Response of Lipid Metabolism to Alterations in Nutritional State. II. The Effects of Overnutrition on the Post Absorptive Levels of the Blood Lipids of the Dog. *J. Biol. Chem.* 142: 129, 1942.
- H22. ENTENMAN, C. E., LORENZ, F. W. AND CHAIKOFF, I. L.: The Effects of Crystalline Sex Hormones on the Blood Lipids of the Bird. *J. Biol. Chem.* 134: 495, 1940.
- H23. FEINBLATT, H. M.: Fat Metabolism. *Am. J. Digest. Dis. & Nutrition.* 11: 260, 1944.
- H24. FLEISHMAN, W. AND SHUMAKER, H. B. JR.: The Relationship Between Serum Cholesterol and Total Body Cholesterol in Experimental Hyper- and Hypothyroidism. *Bull. Johns Hopkins Hosp.* 71: 175, 1942.
- H25. FLOCK, E. V., CORWIN, W. C. AND BOLLMAN, J. L.: Sustained Hyperlipemia of Dietary Origin in the Dog. *Am. J. Physiol.* 123: 558, 1938.
- H26. FRAZER, A. C.: Lipolysis and Fat Absorption. *J. Physiol.* 102: 329, 1943.
- H27. HEYMANN, W.: Renal Hyperlipemia in Dogs. *Science*, 96: 163, 1942.
- H28. HEYMANN, W. AND RACK, F.: Independence of Serum Cholesterol from Exogenous Cholesterol in Infants and in Children. *Am. J. Dis. Child.* 65: 235, 1943.
- H29. INGLE, D. J.: The Relationship of Adrenal Cortex to Fat Metabolism. *J. Clin. Endocrinology* 3: 603, 1943.
- H30. JOELSON, J. J. AND SHORR, E.: Relation of Adrenals to Cholesterol Metabolism. *Arch. Int. Med.* 34: 841, 1924.
- H31. KAPLAN, A. AND CHAIKOFF, I. L.: Effect of Choline in Lipid Metabolism of Blood and Liver in the Completely Depancreatized Dog Maintained with Insulin. *J. Biol. Chem.* 120: 647, 1937.
- H32. KAPLAN, A., ENTENMAN, C. AND CHAIKOFF, I. L.: Effects of Insulin on the Blood Lipids of Man. *Endocrinology* 32: 247, 1943.
- H33. KLOTZ, O. AND BOTHWELL, M. E.: Inhibition of Sodium Oleate Hemolysis and Toxicity by Cholesterin. *Proc. Soc. Exper. Biol. & Med.* 12: 199, 1915.
- H34. KNUDSON, A., STURGES, S. AND BRYAN, W. R.: Cholesterol Content of Skin, Blood and Tumor Tissue in Rats Irradiated with Ultraviolet Light. *J. Biol. Chem.* 128: 721, 1939.
- H35. LEARY, T.: Atherosclerosis. *Rhode Island Med. J.* 25: 173, 1942.
- H36. LEITES, S.: Studien über Fett und Lipidstoffwechsel über die Rolle des retikulo-endothelialen Systems im Fett- und Lipidstoffwechsel. *Biochem. Ztschr.* 186: 391, 1927.
- H37. LEVINE, R. AND SOSKIN, S.: Acid-Base Balance and the Distribution of Fat in the Blood. *Proc. Soc. Exper. Biol. & Med.* 40: 305, 1939.
- H38. LUDEN, G.: Observations on the Changes in the Cholesterol Content of the Blood of Goats Following Cholesterol Feeding Alone, Roentgen Treatment Alone, and Cholesterol Feeding Combined with Roentgen Treatment and Subsequent Castration. *J. Biol. Chem.* 27: 273, 1916.
- H39. MAN, E. B. AND PETERS, J. P.: Permeability of Capillaries to Plasma Lipoid. *J. Clin. Investigation* 12: 1031, 1933.

- H40. MARBLE, A., FIELD, M. E., DRINKER, C. K. AND SMITH, R. M.: The Permeability of the Blood Capillaries to Lipoids. *Am. J. Physiol.* 109: 467, 1934.
- H41. MARINE, D.: Etiology and Prevention of Simple Goiter. *Medicine* 3: 453, 1924.
- H42. MULLER, G. L.: Cholesterol Metabolism in Health and Anemia. *Medicine* 9: 122, 1930.
- H43. OKEY, R.: Effect of Cholesterol Feeding under Varying Conditions upon Lipids of Rat Livers. *Proc. Soc. Exper. Biol. & Med.* 30: 1003, 1933.
- H44. OKEY, R.: Middle and Old Age in Cholesterol-Fed Rats. *Proc. Soc. Exper. Biol. & Med.* 46: 466, 1941.
- H45. OKEY, R., GILLUM, H. L. AND YOKELA, E.: Factors Affecting Cholesterol Deposition on the Tissues of Rats. *J. Biol. Chem.* 107: 207, 1934.
- H46. OKEY, R. AND GREAVES, V. D.: Anemia Caused by Feeding Cholesterol to Guinea Pigs. *J. Biol. Chem.* 129: 111, 1939.
- H47. OKEY, R. AND YOKELA, E.: Effect of Feeding Egg Yolk on Liver Lipids of Young Rats. *J. Nutrition*, 11: 463, 1936.
- H48. PAGE, I. H. AND MENSCHICK, W.: The Destruction of Cholesterol by the Animal Organism. *J. Biol. Chem.* 97: 359, 1932.
- H49. PERLMAN, I. AND CHAIKOFF, I. L.: Radioactive Phosphorus as an Indicator of Phospholipid Metabolism. VII. The Influence of Cholesterol Upon Phospholipid Turnover in the Liver. *J. Biol. Chem.* 128: 735, 1939.
- H50. RAWSON, R. W., HERTZ, S. AND MEANS, J. H.: Thiocyanate Goiter in Man. *Ann. Int. Med.* 19: 829, 1943.
- H51. ROSENHEIM, O. AND WEBSTER, T. A.: Dietary Factor Concerned in Coprosterol Formation. *Biochem. J.* 35: 920, 1941.
- H52. ROSENHEIM, O. AND WEBSTER, T. A.: The Metabolism of  $\beta$ -Sitosterol. *Biochem. J.* 35: 928, 1941.
- H53. SCHÖNHEIMER, R. AND BREUSCH, F.: Synthesis and Destruction of Cholesterol in the Organism. *J. Biol. Chem.* 103: 439, 1933.
- H54. SCHÖNHEIMER, R. AND RITTERBERG, D.: Application of Isotopes to the Study of Intermediary Metabolism. *Science*, 87: 221, 1938.
- H55. SPERRY, W. M.: The Concentration of Total Cholesterol in the Blood Serum. *J. Biol. Chem.* 117: 391, 1937.
- H56. SPERRY, W. M.: The Biochemistry of the Lipoidoses. *J. Mt. Sinai Hosp.* 9: 799, 1942.
- H57. SPERRY, W. M., JAILER, J. W. AND ENGLE, E. T.: Influence of Diet on Cholesterol Content of Blood Serum in Normal, Spayed and Hypothyroid Monkeys. *Endocrinology* 35: 38, 1944.
- H58. SPERRY, W. M. AND STOYANOFF, V. A.: Effects of Long-Continued Cholesterol Feeding in Rats. *J. Nutrition*, 9: 131, 1935.
- H59. SPERRY, W. M. AND STOYANOFF, V. A.: The Effect of Diet on Liver Cholesterol in Chickens. *J. Nutrition*, 9: 157, 1935.
- H60. STEINER, A. AND DOMANSKI, B.: Dietary Hypercholesterolemia. *Am. J. M. Sc.* 201: 820, 1941.
- H61. THANNHAUSER, S. J.: Lipoidoses: Diseases of the Cellular Lipid Metabolism, Oxford Medicine, London, Oxford University Press, 1940, vol. 4, part 1, p. 214(3).
- H62. THANNHAUSER, S. J. AND MAGENDANTZ, H.: The Different Clinical Groups of Xanthomatous Diseases. *Ann. Int. Med.* 11: 1662, 1938.
- H63. TOLSTOI, E.: The Effect of an Exclusive Meat Diet on the Chemical Constituents of the Blood. *J. Biol. Chem.* 83: 753, 1929.
- H64. TREADWELL, C. R. AND ECKSTEIN, H. C.: Sterol Metabolism in Young White Rats. II. The Effect of High and Low Fat Diets on the Cholesterol Metabolism of Four Generations of White Rats. *J. Biol. Chem.* 140: 35, 1941.
- H65. UCHIYAMA, T.: Beiträge zur Morphologie des Lipidstoffwechsels. I. Über die Steatosen der Augenhäute des Haushuhns unter normalen und abnormen Ernährungsbedingungen (Cholesterinölfütterung). *Virch. Arch. f. path. Anat.* 274: 803, 1929-30.



- H66. UCHIYAMA, T.: Beiträge zur Morphologie des Lipoidstoffwechsels. II. Über die Iris- und Ciliarmuskulatur des Haushuhns unter besonderer Berücksichtigung der Verfettung bei normalen und abnormen Fütterungsbedingungen (Cholesterinfütterung). *Virch. Arch. f. path. Anat.* 277: 607, 1930.
- H67. WEINHOUSE, S.: The Blood Cholesterol. *Arch. Path.* 35: 438, 1943.
- H68. WILKINS, L., FLEISCHMANN, W. AND BLOCH, W.: Hypothyroidism in Childhood. *J. Clin. Endocrinology* 1: 3, 1941.
- H69. YAMAGUCHI, M.: Cholesterol Metabolism in Organisms. First Report: The Cholesterol Problem in Regard to Birds. *Jap. J. M. Sc. Abs.* 2: 143, 1925.

# THE EFFECT OF HIGH OXYGEN TENSION ON THE RESPIRATORY SYSTEM<sup>1</sup>

JULIUS KAUNITZ, M.D.

It has been well established in laboratory animals that prolonged and continuous inhalation of an atmosphere containing upwards of 70 per cent oxygen leads to pathological changes in the lungs and eventually death. Binger, Faulkner and Moore (1) state that the poisonous nature of oxygen in such concentration was already known to Lavoisier. Paul Bert (2) showed that atmospheric pressures of over twice the normal accelerated the harmful effects of high oxygen tension, particularly on the nervous system. Lorrain Smith (3) repeated some of Bert's experiments and concluded that lungs were affected by moderately high oxygen tension and the nervous system only by very high oxygen tension. Schmiedehausen (4) and David (5) produced changes at comparatively lower oxygen tension, i.e., 40 to 60 per cent, at normal atmospheric pressure. One of the animals developed pneumonia. Some of the dogs receiving 90 per cent oxygen developed changes in the lungs in from fifteen minutes to one hour; this may have resulted from the tracheal cannula used to administer the gases. Karsner (6) showed that organs in the body other than the lungs were also damaged.

Binger and his coworkers (1), exposing dogs, rabbits, guinea pigs and mice to oxygen concentrations of 70 per cent and over, obtained characteristic reactions in the lungs. These organs were so markedly congested as to resemble liver and to sink when placed in ten per cent formalin solution. Microscopic examination disclosed: (a) capillary engorgement with hemorrhage, (b) serum and mononuclear cells in the interstitial and intra-alveolar spaces, and (c) hypertrophy and desquamation of alveolar walls. These findings agree with those of most other authors. Apparently the pneumonia described by some investigators does not belong to the picture, but is either due to coincident infection, or to intense congestion. Culture of the lungs by Binger and his coworkers did not demonstrate bacteria. Furthermore, there was no infiltration with polymorphonuclear cells.

The writer's experiments were conducted with 30 mice at atmospheric pressure. There was a free flow of 100 per cent oxygen into the chamber, and carbon dioxide was removed by soda-lime. All the animals were apathetic at the end of the second day, manifesting no interest in food or drink. On the third day they became markedly dyspnoeic and cyanotic and died, some in convulsions.

## ANATOMICAL FINDINGS

*Gross:* The lungs were collapsed, dark red, had the consistency of liver and sunk to the bottom of the formalin solution. The heart, liver and kidneys were dark red and swollen.

<sup>1</sup> From the Laboratory of Beth David Hospital.

*Microscopic:* (fig. 1) A section of trachea showed marked interstitial edema and the mucosa was completely denuded of epithelium. (fig. 2) The walls of the bronchi were edematous and the lumen was filled with epithelial cells, erythrocytes, transudate and detritus. The surrounding parenchyma was atelectatic, the thickened alveolar walls containing enormously engorged capillaries. The alveolar spaces were filled with transudate, erythrocytes and fibrin. In some sections the alveoli appeared dilated, probably due to spastic or partially obstructed bronchi, as in obstructive emphysema. No polymorphonuclear leucocytic reaction was noted.

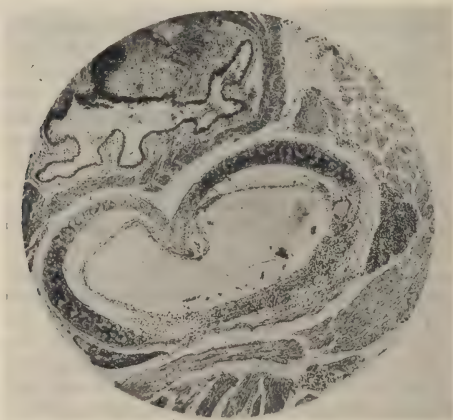


FIG. 1. Section of the trachea showing marked interstitial edema. The mucosa is completely denuded of epithelium.

The pathological changes in the respiratory tract are primarily due to the prolonged irritative effect of the oxygen. Clinically and morphologically the reaction may be compared with that of some of the war gases. Cameron (7) clinically, and Short (8), experimentally, in a study of phosgene and other irritant gases, described the presence of mucus secretion, bronchial spasm and obstruction, epithelial desquamation, pulmonary collapse, capillary dilatation, plasma exudation and heart failure.

At the outset, oxygen reaches the alveoli with ease. Later, the bronchi show contraction and become filled with mucus and desquamated epithelial cells which obstruct the air passages. The intra-alveolar gases are absorbed, and as no more air enters, the pulmonary segment dependent on the obstructed bronchus collapses. It was demonstrated previously (9) that with the drop in intra-alveolar pressure there is dilatation of the capillaries with transudation into the alveolar

spaces of plasma alone or plasma with formed blood elements, depending on the degree of capillary permeability. The concentrated oxygen, however, is sufficiently irritating to cause marked vascular congestion of the alveoli, and we may assume that this is an important contributory factor.

The pulmonary collapse, edema, and capillary stasis all encroach upon the vital capacity until the oxygenation of the blood is inadequate for life. We thus have the paradox of anoxia caused by high oxygen tension. Despite the harm caused by the pure oxygen, the animals are dependent upon it to such a degree that transferring them to a normal atmosphere at any time during their last six hours of life brings on instant death.

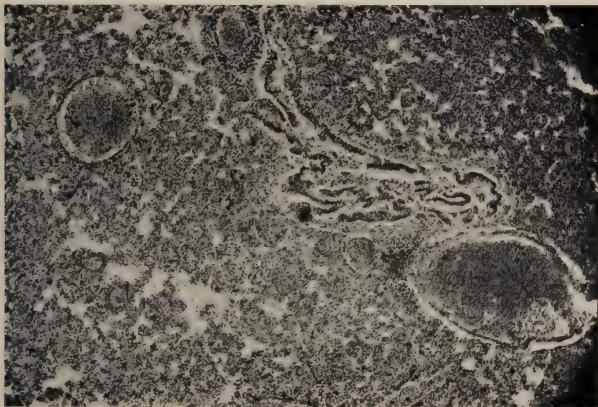


FIG. 2. Section of a lung showing a large bronchus with edematous walls and its lumen filled with exfoliated epithelium, erythrocytes, transudate and detritus. The surrounding parenchyma is atelectatic. The capillaries of the thickened alveolar walls are engorged and the alveolar spaces are filled with transudate, erythrocytes and fibrin.

Anoxemia occurring during exposure to high oxygen tension results in damage to organs other than the lungs. Diffuse and severe myocardial damage has been reported elsewhere by the writer (10).

Binger and his coworkers were the first to report that the death of the animals in abnormal oxygen tensions results from oxygen want. They believe that the hypoxia is due to damage of the diffusion membrane of the lungs which interferes with proper oxygenation of the blood. To this we should add other more or less important factors, namely, (a) diminished vital capacity due to atelectasis, pulmonary edema and stasis, and (b) diminished cardiac output, due to pulmonary capillary stasis, myocardial degeneration and congestive heart failure.

## DISCUSSION

We have very little knowledge of the effect on human beings of inhalations of 100 per cent oxygen over prolonged periods. The concentration rarely exceeds 60 per cent when oxygen is administered by tents, nasal catheters or masks, and when high pressure helmets or masks which insure 100 per cent oxygen are employed, they are frequently removed for purposes of feeding, washing, etc. For this reason most reports on the harmless effects of 100 per cent oxygen over prolonged periods are of no value.

In some studies on the inhalation of 100 per cent oxygen by healthy men, Behnke (11) found that some suffer no injurious effects after 17 hours. Others however complain of substernal distress and irritability after 7 hours. In one individual a sensitivity was manifested as evidenced by wheals, dermographism and flushing of the face followed by a dermatitis. At a pressure of 3 atmospheres in which the effects of oxygen is considerably augmented, his subjects suffered nausea after a few hours. After four hours there was also a facial pallor and a progressive contraction of the visual field terminating in a transient amblyopia.

Becker-Freyseng and Clamann (12) studied the effect of 90 per cent oxygen on themselves in an air tight chamber for sixty five hours. During the first 24 hours neither suffered any discomfort. On the second day however they both began to feel uncomfortable. Symptoms such as malaise, dyspnoea, rise in temperature, accelerated pulse and paresthesia of the finger tips were noted; the paresthesia lasted ten days. One of the experimenters developed the physical signs of bronchopneumonia.

It is obvious that a high concentration of oxygen acts as an irritant to the respiratory tract. Therefore despite our meagre knowledge of its action on human beings exposed for prolonged periods, it might be assumed that its effects would not differ materially from those obtained in experimental animals.

## CONCLUSION

The results of inhalation of oxygen at high tension are, in a measure, similar to those produced by irritant gases on the respiratory tract.

Mice exposed to 100 per cent oxygen for three days developed interstitial edema of the trachea, bronchi and lungs, denudation of the epithelium of the trachea and bronchi, as well as constriction and occlusion of the bronchi associated with atelectasis. These pathological changes were followed by progressive anoxemia, causing damage to the myocardium and other vital tissues.

## BIBLIOGRAPHY

1. BINGER, C. A. L., FAULKNER, J. M., AND MOORE, R. L.: Oxygen poisoning in mammals. *J. Exper. Med.* 45: 849, 1927.
2. BERT, PAUL: *La Pression Barometrique*, Paris, 1878.
3. SMITH, J. L.: The pathological effect due to increase of oxygen tension in the air breathed. *J. Physiol.*, 24: 19, 1899.
4. SCHMIEDEHAUSEN, P. G.: *Die Pathologisch-anatomischen Veränderungen der Lungen bei verändertem Sauerstoffgehalt der Atemluft*. Inaugural Dissertation, Halle, 1909.



5. DAVID, O.: Versuche zur Erzeugung von Lungenhyperämie. *Ztschr. f. klin. Med.*, 74: 404, 1912.
6. KARSNER, H. T.: The pathological effects of atmospheres rich in oxygen. *J. Exper. Med.*, 33: 149, 1916.
7. CAMERON, G. R.: Symposium on lung injuries in air raids. *Brit. M. J.*, 2: 241, 1941.
8. SHORT, R. H. D.: Symposium on lung injuries in air raids. *Brit. M. J.*, 2: 241, 1941.
9. KAUNITZ, J.: Obstructive atelectasis. *Bull. Sea View Hosp.*, 2: 290, 1937.  
KAUNITZ, J.: Dry and wet stages of obstructive atelectasis. *J. Thoracic Surg.*, 7: 512, 1938.
10. KAUNITZ, J.: Myocardial damage resulting from high oxygen tension. *J. Aviation Med.*, 13: 267, 1942.
11. BEHNKE, A. R.: Physiological studies pertaining to deep sea diving and aviation especially in relation to the fat content and composition of the body. *The Harvey Lecture. Bull. New York Acad. Med. series 2*, 18: 561, 1942.
12. BECKER-FREYSENG, H., AND CLAMANN, H. G.: Zur Frage Dr. Sauerstoffvergiftung. *Klin. Wehnschr.*, 18: 1382, 1939.

## RECENT ADVANCES IN CELLULAR PATHOLOGY\*

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It is the object of pathologic anatomy to define disease in terms of organ and tissue alterations. In the evolution of this fundamental aim, pathologic anatomy has progressed from the primary gross descriptive method of Morgagni to the most detailed microscopic analysis of cellular alterations, inaugurated by Virchow. The correlation of disturbances of function with alterations of form and structure has been the cornerstone of scientific medicine. For more than half a century medical research was conducted mainly along morphologic lines. However, the rapid advances in bacteriology and immunology, the application of exact chemical and physical methods in the analysis of functional disturbances led to a reorientation of medical science. Pathologic anatomy was censured of being concerned with the final phases of disease only. The recognition of static structural alterations was still accepted as a valuable aid in diagnosis, pathologic anatomy still retained its position in the teaching of medicine but it seemed agreed upon that it could not greatly contribute to the solution of the fundamental problems of disease—etiology and pathogenesis. Morphologic investigations were appreciated only so far as they contributed to experimental pathology. The proponents of the dynamic approach to disease seemed to have forgotten that, to use the words of Virchow, “an unbiased anatomic perception permits of the recognition of causal relationships”, and “that the experiment is only the control for the pathologic anatomic conclusion.” They also seemed to have lost sight of the historical fact that experimental pathology as well as pathologic physiology could develop only on the firm foundation of an exact morphologic doctrine.

Pathologic anatomy has proceeded without concern along the lines of morphologic investigation. The decline in esteem has not affected its contribution to the progress of medicine.

If I were to report on its accomplishments in recent years, I would not lack in material. Tonight, however, I should like to review with you certain investigations of microscopic anatomy which represent, in my opinion, a distinct recent advance in the role which cellular pathology can play in the progress of medical science. In my selection of particular lines of research I was guided not only by their actual results but also by a consideration of their methodical value for future investigations.

The correlation of structure and function is the essence of morphologic research. Every discovery of a structural detail in the cell arouses the question as to its functional significance. It is evident that comparison of finer cell details, such as mitochondria and Golgi apparatus under normal and pathologic conditions could greatly contribute to our understanding of normal and path-

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ologic cell functions. Unfortunately, cytological investigations demand not only a highly developed technique but also are dependent upon a state of vital preservation not easily obtained in human pathologic material. The number of reports on mitochondrial studies in human pathologic material is very high. Unfortunately, the information obtained is not much greater than that which one gains from a careful examination of cytoplasmic changes with less complicated methods of histologic technique.

Investigations of the Golgi apparatus under various biologic conditions have revealed certain information correlating the size of the apparatus with the physiologic activity of the cell. It has been established that in exocrine glands the Golgi body hypertrophies during secretory activity. There is experimental evidence that activation of endocrine glands also results in hypertrophy of the Golgi apparatus. This occurs, for example, in the thyroid gland after the injection of anterior pituitary extracts, in pancreatic islet cells after oestrone injection, and in the rat parathyroid after the experimental induction of low calcium and low phosphorus rickets, respectively. Hypertrophy of the Golgi apparatus in the thyroid of Graves' disease has been reported by Welch and Broders in 34 out of 35 cases and in adenomatous goiters with hyperthyroidism in 19 of 21 glands. Hypertrophy of the apparatus was also found in 5 of 16 adenomatous goiters in patients who were not judged to have hyperthyroidism. A marked polarization of the Golgi body is generally a characteristic of exocrine gland cells, the apparatus being between the nucleus and the surface at which the secretory products are discharged. The only endocrine gland which shows anything like a fixed polarity is the thyroid, where the body is between the nucleus and the follicular lumen. Cowdry maintained that the position of the Golgi body was a reliable index of the direction of secretory release, its occasionally reversed position in the guinea pig, for example, being indicative of secretion directly into the capillaries. This concept has not been generally accepted and the question of the polarity of the Golgi body in endocrines is still highly controversial.

Severinghaus distinguished a characteristic Golgi apparatus within the cells of the pituitary. The basophilic elements are distinguished by a ring, the acidophilic by a filamentous net. The predetermination of the change of the chromophobe cell into a basophilic or eosinophilic element is indicated by the morphology of the Golgi body in the mother cell. These observations are of practical importance because they could be applied in such instances of acromegaly in which an apparently chromophobe cell adenoma is found at autopsy instead of the anticipated eosinophile cell tumor. This, though a very incomplete survey on the internal reticular apparatus of Golgi as applied to human pathology, certainly does not encourage much hope as to the practical value of such painstaking cytologic research in the morphologic analysis of human disease. But the interesting reports of recent years in another field of histiophysiologic research should be reassuring.

Since the demonstration of characteristic granules in the cells of the islands of Langerhans by Lane and Bensley, the B cells have always been considered as being concerned in insulin production. The investigations of Ham and Haist

have demonstrated that anterior pituitary extracts injected in daily doses into dogs cause progressive degranulation and hydropic degeneration of the B cells by stimulating these cells to excessive function. On the other hand, we have now available a chemical substance Alloxan, the ureide of mesoxalic acid, which seems to have a direct deleterious effect upon the B cells. In larger doses it causes necrosis of the islands of Langerhans in rabbits, while smaller doses, particularly in dogs, produce selective degranulation of the B cells and clinical diabetes. The simplification of the histologic technique for the demonstration of the B and alpha granules by Gomori has facilitated the investigation of human material. The routine examination of the pancreas from unselected cases, for the presence of these granules should produce interesting results.

The proliferation and changes in the ratio of the hypophyseal cells provoked by removal of other endocrine glands, or by hormonal injection, further exemplify the result of recent studies in cellular pathology and their significance in endocrinologic research.

I should like to turn now to another chapter of histologic research which in recent years has aroused the interest not only of the histologist but also of the physiologist.

In 1925 Ruyter observed in the mouse large granular cells within the wall of the afferent arteriole as it approaches the glomerulus. He described them as epithelioid in nature with round or oval nuclei in contradistinction to the elongate nucleus of the smooth muscle. The cytoplasm is unfibrillated and rich in granules. Where these cells are present, smooth muscle may be entirely absent and they have an abundant nerve supply. Ruyter believed that they are derived from smooth muscle. He compared them with the epithelioid cells in arteriovenous anastomoses. He considered these cells to be a constituent of the normal mouse kidney and found them in rats also, but not in the monkey, cat, rabbit, guinea pig, or man. Oberlin, in 1927, described similar cells in the human kidney, which he thought were identical with the neuromuscular cells of digital glomi.

In 1932 Goormaghtigh described cells of an epithelioid nature in the afferent arterioles of the human kidney which differed from Ruyter's cells in having no, or at most, very few granules.

This juxtaglomerular neuro-myoarterial apparatus has subsequently been described by other histologists and certain new information has been added, particularly as to its topography between the glomerular capsule and the pertinent distal convolute tubule. I shall not enter into further histologic description of these details which can be found in the original articles and in Homer Smith's Harvey lecture.

The juxtaglomerular apparatus has been considered as exerting a delicate regulatory mechanism upon glomerular circulation. Goormaghtigh believes it to be an endocrine organ, the main function of which is the secretion of a pressor substance, possibly renin. He found striking hypertrophy of the granular cells in dogs and rabbits made hypertensive by the Goldblatt technique. Opposing this belief, Oberling maintains that in the human, identical pictures are never

observed and that contrary to Goormaghtigh's hypothesis, in severe hypertension the granular cells generally degenerate. Consequently, he assumes that the degeneration of the apparatus is responsible for the suppression of a regulatory mechanism, which in turn may account for the development of hypertension.

While these lines of histiophysiologic research take their origin from the identification of structural elements within the organs, another chapter of morphologic research was stimulated by the advance of enzyme chemistry and intends to visualize the site of enzyme activity within tissues. Ehrlich's and Unna's investigations of the site of oxydative processes within cells were the starting point for the discovery of the oxydase reaction by Winkler and Schultze and the demonstration by Löle of a stable and a labile oxydase within the animal body. The presence of the stable oxydase in blood cells is used, as you know, for the identification of myeloid elements. The instability of the other oxydase, however, has handicapped its further investigation with morphologic methods.

The discovery by Bruno Bloch of the specific dioxyphephenalaninoxydase, Dopaoxydase, has clarified the site and mechanism of pigment formation in the human and animal body.

The technique described very recently by Takamatsu and by Gomori for the histochemical demonstration of phosphatase is specific for this enzyme. Alkaline phosphatase activity is characteristic of certain cells. Among normal cells the epithelium of the small intestine and of proximal convoluted tubules, osteoblasts and endothelium are particularly rich in phosphatase.

The stability of this enzyme and the simplicity of its histologic demonstration justify the hope that investigations on human pathologic material will yield valuable results.

Oster and Schlossman in our laboratories have demonstrated the presence of an amino-oxydase within the cells of the distal convoluted tubules of the guinea pig kidney. It could be suggested that this enzyme might be utilized in the deamination of circulating pressor amines and become inactive in ischemia of the kidney. However, the absence of this enzyme in the rat's kidney, as shown by the authors, casts, according to them, doubt on the general validity of the amino-oxydase theory of nephrogenic hypertension.

The techniques, so far reviewed, are only qualitative ones permitting mainly of the localization of enzymatic action although the intensity of the reaction might be utilized as an index of quantitative factors. The complicated technique employed by Linderstrom Lang, and his school, compares in successive equal frozen sections the cellular composition with enzymatic activity. With this method the distribution of pepsin, dipeptidase, and urease in the swine's stomach and arginase in the kidney of the rabbit has been studied. Glick and Biskind have applied the same method for the study of the distribution of Vitamin C in the adrenal gland.

If I now turn to a review of the cell and tissue changes in avitaminosis I should like to remind you that Vitamin A can be demonstrated by its fluorescence when present in tissues.



In the further discussion I should like to limit myself to the cell and tissue changes observed in Vitamin A and C deficiencies. The reason for this selection is that only in these states the rationale of the morphologic alterations is clarified, whereas in the other deficiencies we have not yet passed beyond the mere descriptive phase of information.

We owe to Wolbach and his associates not only the most comprehensive description of the structural alterations in Vitamin A and C deficiency states, but also the most adequate elucidation of the biological principles of their development and recession. These investigations illustrate how the searching morphologist can penetrate to the very foundations of the living substance.

The effect of Vitamin A deficiency is exhibited mainly in alterations of epithelium and teeth. Descriptively they are manifest in keratinizing metaplasia of the salivary glands, the respiratory tract, the genitourinary system, eyes, and paraocular glands. Vitamin A deficiency also produces profound changes in the incisor teeth of rats and guinea pigs. Their growth and organization throughout the life of the animal is controlled by the enamel organ, an epithelial organ which in Vitamin A deficiency atrophies and undergoes keratinizing metaplasia.

The fact that such heterogenous epithelium like that of salivary gland and Fallopian tubes react in an identical way is accounted for by Wolbach that both have a secreting function in addition to the role of a covering layer and that the functioning cells are without power to divide and therefore unable to regenerate. Repair therefore must take place from basal cells. Vitamin A, according to Wolbach, may form within the covering epithelial cells a vitamin-protein compound like it does in visual purple. This vitamin-protein compound may constitute a cell apparatus concerned with the specific chemical function of the cell. In its absence, due to vitamin deficiency, the specific cells atrophy while the germinal cells proliferate but in an undifferentiated form. Upon restoration of Vitamin A to the deficient animals the differentiated epithelium returns. This proves that the stratum germinativum preserves the identity of the original epithelium throughout the period of metaplasia. The significance of these investigations for a deeper knowledge of cellular biology can best be demonstrated by quoting from an article by Wolbach and Howe.

"The evidence is conclusive that all the cells of the stratum germinativum can assume the original functions and morphology without undergoing division when supplied with Vitamin A. We may therefore conclude that the nuclear chromatin remains unaffected by the deficiency. We believe that careful cytological studies as the deficiency progresses and during the recovery phenomenon may yield interesting correlation between morphology and function. In 1925 we concluded that the mitochondrial apparatus was not the seat of the primary injury in A deficiency and suggested that nuclear changes were important. Obviously, if there are two sorts of chromatin, one concerned with identity (idiochromatin), the other with cell function (trophochromatin) we have in the cycle of A deficiency metaplasia and recovery, a possible means of securing appropriate material for this study."

While these studies of Vitamin A deficiency have provided us with fundamental information of the pathomorphology of epithelial cells, the investigation of Vitamin C deficiency states has supplied equally important revelation concerning the morphogenesis of the connective tissues. The alterations which these tissues undergo in complete scorbutus and in recovery states have given us a deep insight into the formation of these tissues and have decided problems which have vexed histologists and pathologists for many decades.

From these and other investigations by Wolbach and his associates scorbutus can be defined as a condition characterized by the inability of the connective tissues to produce and maintain intercellular substances. The following conclusions can be reached as to the formation of the intercellular substances: The mesenchymal cells endowed with the production of intercellular substance produce a liquid material which, under the influence of an agent present in vitamin C, undergoes a process of setting or jelling. Within this collagenous ground substance fibers are formed under the organizing influence of fibroblasts.

It is certainly not a coincidence that these investigations on scorbutus have been contemporaneous with an intense interest of pathologic anatomists in alterations of the connective tissues in other human diseases. The investigations of Klinge and Rössle of rheumatic fever have demonstrated that lesions of the connective tissue throughout the body and especially alterations of the intercellular substance are of fundamental importance in the pathomorphology of this malady. The study of the pathology of disseminated lupus erythematosus and scleroderma, which we have carried out in the past years, has focused our attention upon the collagenous tissue of the body.

These observations demonstrate that the basic structural changes in disseminated lupus and scleroderma reside within the connective tissue system of the body. But the visible alterations of this system are only the most pronounced manifestations of a disturbance of the colloidal connective tissue system and different degrees of this imbalance might obtain beyond the power of our microscopes to reveal. To determine such states with methods other than optical must be the object of further investigations; to correlate such physical—molecular—aberrations with functional disorders and with cause must be our final aim in order that we reach a full understanding of the fundamental nature of these obscure maladies. Analytical morphologic investigations can point the way, but only the cooperation of all lines of medical research can lead to synthesis.

## THE CLINICAL SIGNIFICANCE OF PAIN IN ACUTE CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION

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The association of pain in the chest with heart disease has been uppermost in the minds of the laity and the medical profession ever since the classic description of Angina Pectoris by Heberden (19) in 1768. Since then it gradually became recognized that pain in the chest, which is more severe and persistent in nature, may be associated with coronary occlusion.

Herrick (20), in 1912, in discussing the "clinical features of sudden obstruction of the coronary arteries," stated that although the pain in the chest associated with coronary thrombosis may be of unusual severity, yet "the clinical manifestations of coronary obstruction will evidently vary greatly, depending on the size, location, and number of vessels occluded . . . . In some instances there has been no definite radiation of the pain, as to the neck or left arm, though this may have been a feature of other anginal attacks, and the pain may be referred to the lower sternal region or definitely to the upper abdomen." At this time he already noted that there may be cases of coronary occlusion with little or no pain.

Astute clinicians for a long time have recognized that not all patients have pain, nor do all react to the same disease in a similar manner. Libman (31) in his "Observations on Sensitiveness to Pain" aptly stated that "clinical experience shows that patients are not equally sensitive to pain and that the same disease may cause varying clinical pictures in different persons." In 1919 before the Association of American Physicians Libman (30) noted that "when thrombosis of a coronary artery occurred in a patient who was not sensitive to pain, pain could be absent." Further he found that "acute coronary thrombosis of even fatal type may occur without pain if the sensitiveness of the patient be low. In older cases of thrombosis, and in cases of narrowing of the coronary arteries, there may be present little or no pain in the patient who is not sensitive."

Again in 1929, Libman (32) pointed out that "while the sensitive and the hyposensitive patient may have the same symptomatology in a given disease, that of the hyposensitive is often different. Briefly stated, the hyposensitive individual is apt to feel less or none of the pain characteristic of the disorder, to have much more of the substitution symptoms, more of the peculiar radiations of pain, and more in the way of reflex symptoms. Whereas a mild clinical picture in a sensitive person usually points to a milder form of disease, it may, in a hyposensitive one occur in the presence of severe conditions." He also stressed the fact that "one must magnify in his mind the mild symptoms of a hyposensitive if one wishes to calculate their real significance." Thus Libman found that in hyposensitive patients suffering an attack of coronary thrombosis, dizziness and vertigo may take the place of usual gastric disturbances such as nausea and

vomiting. He also found that "in hyposensitives, the pain may be slight or absent, and be replaced by the substitution symptoms such as burning, a sense of pressure, a feeling of constriction in the chest or in the throat, a feeling of swelling of the arms or forearms, etc. In the hyposensitive individual epigastric localization is of more frequent occurrence. Dyspnea may become the outstanding complaint. Other symptoms may become predominant, such as coldness, sweating, weakness of the extremities, general weakness, collapse, etc."

Since the observations of Herrick and Libman, it has been amply confirmed that coronary occlusion may occur with little or no pain. There has appeared in the literature a number of papers on the incidence of painless coronary occlusion (2, 39, 22, 46). There is a wide divergence of opinion as to the frequency of coronary occlusion without pain. Thus it has been reported to occur without pain on the one hand as high as 75 per cent, and on the other hand as low as less than 1 per cent. Another paper merely on the incidence of coronary thrombosis without pain would serve no useful purpose. Our own observations on certain cases has given us an insight as to some of the reasons which might account for such a wide divergence of opinion in the literature.

Morawitz and Hochrein (37) in a study of 91 cases of coronary thrombosis found 75 per cent to be without pain. Bruenn, Turner and Levy (7) report 61 per cent of a series of 31 cases with no pain. Gorham and Martin (14) in the study of 100 cases found that painless coronary occlusion occurred in 42 per cent of their cases. Saphir, Priest, Hamburger and Katz (42) report 38 per cent of their cases of coronary thrombosis to be without pain. Boyd and Werblow (6) in a study of 127 cases found one third without pain, while Stroud (46) in the study of 49 cases of proven myocardial infarction found 26.5 per cent without pain.

On the other hand there is another group of investigators who have found that acute coronary occlusion without pain is rare. Kennedy (22) who has studied 200 cases of coronary thrombosis found that in the acute cases only about 4 per cent had no pain or distress in the chest. Pollard and Harvill (39) "in a study of 375 cases of myocardial infarction in which the diagnosis was based on clinical features, electrocardiographic findings, and available necropsy material, there were 17 instances (4.5 per cent) of undoubted coronary occlusion in which no pain, substernal pressure or other "anginal" symptoms had occurred at any time." Rosenbaum and Levine (28) in a study of 208 patients found there were 4 who had no pain or sense of oppression at all and 2 more in whom pain was thought to be absent but whose history was not satisfactory. Thus, at most, 3 per cent of the patients had "painless myocardial infarction." Paul D. White (48) also agrees with Kennedy, and in his own observations and experience he found myocardial infarction without pain relatively rare. Dr. C. F. Roche (41), who has been interested in the same problem, found from his own records that "it would be extremely surprising if he had more than 4 per cent unquestionable cases without pain." Babey (2) in a study of 116 cases was able to find only one case without pain, and according to his experience feels that painless acute infarction of the heart is a rarity.

In a review of my own material I have considered no case of acute coronary occlusion as painless if there were symptoms such as burning, a sense of pressure, a feeling of constriction of the chest or in the throat, choking, tightness or simple heaviness in the chest, or a feeling of swelling or numbness in both arms. The foregoing are the substitution symptoms for pain which Libman found in the hyposensitive group. In a study of 350 cases of coronary occlusion with myocardial infarction, we have found only 10 cases which could have been considered to have occurred without pain. This is an incidence of less than 3 per cent.

Although we have seen cases of acute coronary occlusion without pain, nevertheless we have never seen acute coronary occlusion and myocardial infarction without pain unless it was accompanied by some other subjective symptoms.

Our experience with such a case without pain and apparently without any symptoms focused our attention to this problem:—

#### REPORT OF CASES

*Case 1. History:* P. S., a manufacturer in Georgia, came to the office on January 7, 1943 at the recommendation of his brother for a "check-up," and stated that he was feeling fine. His past history was negative except that about 20 years previously he was told that he had a heart murmur, and 17 years previously he was given life insurance, but at an increased rate. There was no history of rheumatic fever, tonsillitis or scarlet fever.

*Examination:* A man about 5' 5", weighing 141 lbs. and of good color. The pupils were equal and regular, and they reacted to light and accommodation. The retinal vessels showed some slight sclerosis. On fluoroscopy, the heart was normal in size, shape and position.

*Laboratory data:* The blood pressure was 144 systolic and 90 diastolic and pulse rate, 72. The heart sounds were of good quality. There was a rough systolic murmur at the apex. The pulmonic second sound was greater than the aortic second sound. The peripheral vessels in both legs were patent, and the oscillometric reading was 6 units in both legs, which was well within normal limits.

A stethogram taken on the same day revealed tracings which is suggestive of a presystolic and systolic murmur (fig. 1). The electrocardiograms taken on the 1st day (fig. 2) showed a slight depression of the S-T segment in lead I, and a cove plane inversion of T<sub>1</sub>. There was a diphasic and partially inverted T<sub>2</sub>. The Q waves were prominent in leads II and III, and a slight elevation of the S-T take off in lead IV with a diphasic T wave. The unexpected finding of these abnormal electrocardiograms in a man without any signs or symptoms prompted us to repeat another electrocardiogram which was identical.

A blood count taken on January 7 showed the white cell count to be 15,050. The sedimentation time on January 9th was 25 mm. (corrected) in one hour by the Wintrobe method.

After repeated questioning, the patient stated that he was entirely free of symptoms. He was markedly hyposensitive when examined according to the Libman technique.

The problem was presented to the patient, who did not believe that there was anything wrong with him. He finally consented to enter the St. Francis Hospital of Miami Beach on January 10, 1943 for observation. While there, he would not stay in bed, walked around, smoked cigarettes, and took his own baths; at no time was he convinced that he was sick.

The following are blood pressure readings taken while he was hospitalized: January 11—128 systolic and 90 diastolic; January 12—126 systolic and 90 diastolic; January 13—160 systolic and 90 diastolic; January 14—160 systolic and 90 diastolic; January 15—132 systolic and 90 diastolic; January 16—140 systolic and 90 diastolic. The following are laboratory findings covering the same period: January 11—complete blood count revealed hemoglobin, 92 per cent; red blood count, 4,740,000; white blood count, 11,700; differential, lymphocytes,



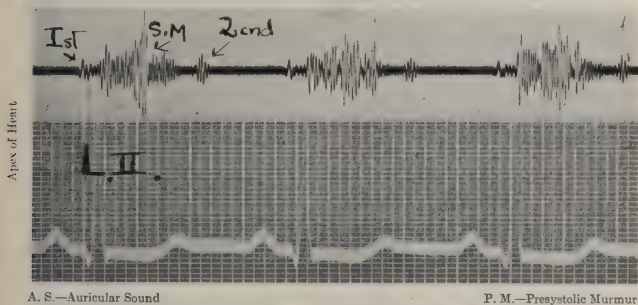
36 per cent; polymorphonuclear, 58 per cent; eosinophils, 3 per cent; monocytes, 2 per cent; plasma cell, 1 per cent. The blood sedimentation rate was 1.26 (corrected) by the Ernestene-Rourke method (0.65 normal). The urinalysis was negative. January 12—nonprotein nitrogen was 61.8 mg. per 100 cc.; fasting blood sugar was 102.0 mg. per 100 cc.; blood cholesterol was 167.5 mg. per 100 cc., and the Kahn test was negative. Jan. 16—the white cell count was 14,850.

The electrocardiogram taken on January 13th showed a cove shaped S-T interval with an inverted T in lead I. Lead II showed a small Q wave, normal conduction times and an upright T. Lead III showed a Q wave of 3 mm. and a slightly elevated S-T segment with an upright T. Lead IV showed a P wave of very low voltage with slurring and a slightly elevated S-T segment with an upright T.

He was seen in consultation with Dr. C. F. Roche on January 13, 1943, who confirmed my findings that the patient was asymptomatic and was suffering from coronary artery

S. M.—Systolic Murmur

D. M.—Diastolic Murmur



A. S.—Auricular Sound

P. M.—Presystolic Murmur

Fig. 1. Simultaneous stethogram and electrocardiogram

thrombosis (anterior wall). The patient had absolutely no symptoms. He had a grade 2 systolic murmur—now suggestive of A. S. type which the patient said had been in existence for twenty years.

*Course:* Had this patient left Miami Beach, I think we would have been justified in assuming that the case was one of coronary occlusion with myocardial infarction not only without pain, but also without any symptoms. Fortunately he remained as advised in southern Florida. Although he continued to claim that there was nothing ever wrong with him, his wife revealed that about five or six years ago he had had an attack of pain in his left shoulder, which was then thought to be "bursitis" (11). At this time he was able to move his left arm freely, and the pain disappeared in a few days after short wave therapy. His wife noticed that after this attack of "bursitis" he used to come home fatigued. On closer questioning, it was found out that his recent trip to Florida was not merely for a vacation, but for a needed rest since he was again beginning to feel very tired, sluggish, and exhausted at the end of a day's work in the past few months. Also, he had a sense of fullness in his chest after eating.

On February 6, 1943 I was called to see him. Contrary to instructions, he walked a distance of about 7 to 8 blocks, and he felt extremely weak in his legs and had a feeling of coldness. For the first time he realized that he was not well. His blood pressure then was 158 systolic and 90 diastolic. On February 12 while talking to a group of people, he became excited and had a sense of choking. At this time he recollected that about two weeks

previously he had a sense of pressure in his chest with peculiar sensations down both arms. On February 15 there was further excitement in the hotel, and the patient again became upset. His blood pressure rose to 180 systolic, and 100 diastolic, and he had definite complaints of precordial oppression.

The laboratory findings during this period were as follows: January 23—the white cell count was 15,150 with 25 per cent lymphocytes and 69 per cent polymorphonuclear. The blood sedimentation rate was 30 mm. (corrected) in one hour by the Wintrobe method. January 30—the white cell count was 14,600 and the blood sedimentation rate 32 mm. (cor-

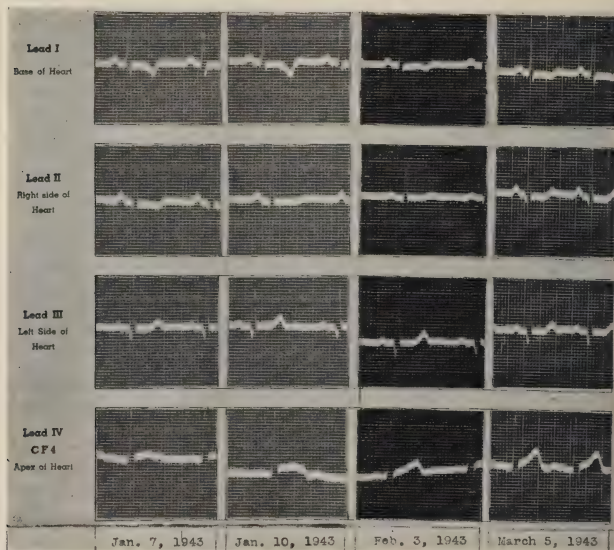


FIG. 2. Serial electrocardiograms showing progressive "T" wave changes. See figure 3 for latest records.

rected). February 15—the sedimentation rate was 23 mm. (corrected). February 27—the white cell count was 13,850 and the blood sedimentation rate 19 mm. (corrected).

The electrocardiograms in the meantime showed progressive changes toward improvement. The inverted T wave in lead I became less shallow, and in lead II it became upright, and by March 5th there was little evidence of myocardial damage except for an inverted T wave in lead I and prominent Q waves in leads II and III (fig. 2).

In all probability this patient had his coronary occlusion for some time before he presented himself for examination. The increased sedimentation rate, leukocytosis, transient drop in blood pressure, as well as the serial changes in the electrocardiograms indicated that his myocardial infarct had not healed. It is possible that in this case we were dealing with a gradual occlusion or a series of minor occlusions. We interpreted the valvular lesion as an old healed mitral stenosis of rheumatic origin.

On March 29, 1943 the patient was very much improved, and he left Miami Beach for his

home. On February 18, 1944 we received a distance telephone message from the patient's wife in Georgia, informing us that her husband was suffering now from high blood pressure, sensory disturbance in the right arm, and the vision in the left eye was deteriorating. On April 26, 1944 the patient came back to Miami Beach complaining of a peculiar lack of sensation in the right arm and lack of vision in the left eye. Although he claimed that he was feeling fine, nevertheless he walked in with a cane, and admitted after further questioning that he had marked weakness and could not walk more than a block without exhaustion. His blood pressure was 210 systolic and 90 diastolic, pulse, 72 and weight, 137 lbs. Exam-

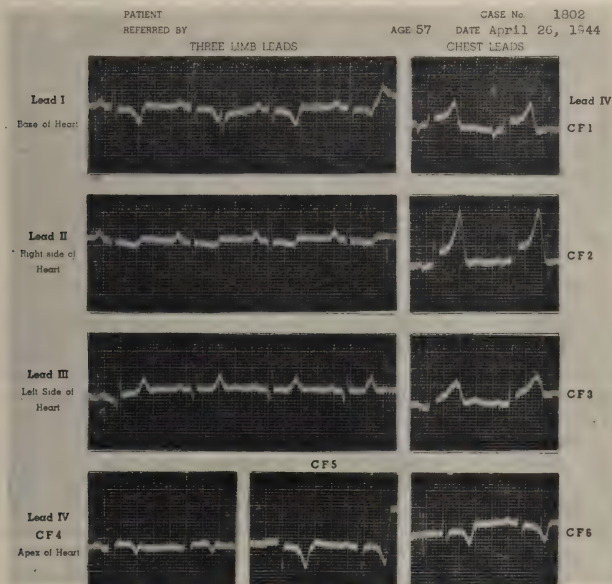


Fig. 3. Electrocardiograms with chest leads showing changes characteristic of coronary occlusion and myocardial infarction.

ination of the eyes disclosed that vision in left eye was impaired, he could see fingers at 2 ft. with no improvement with correction. The fundus of the left eye showed a diffuse hemorrhagic retinitis and a thrombosed central vein. The right fundus showed a small, punctate hemorrhage of the superior-temporal branch.

The sedimentation rate was 18 mm. (corrected) in one hour by the Wintrobe method. The electrocardiogram taken on this date with six chest leads showed a slight depression of the S-T segment in lead I and a cove plane T wave, a diphasic and slightly inverted  $T_2$ , prominent Q waves in leads II and III, and cove plane, inverted T waves in  $CF_4$ ,  $CF_5$  and  $CF_6$  (fig. 3). The patient stayed in Miami Beach until the end of May, and with rest and medication his blood pressure came down to 144 systolic and 90 diastolic.

On July 10, 1944 he went to New York and saw Dr. George Baehr, who confirmed my

findings of probable preexisting coronary artery thrombosis from which he was now convalescing.

COMMENT. This most instructive case has been presented in detail because it emphasizes what Libman has already stated that "one must magnify in his mind the mild symptoms of the hyposensitive if one wishes to calculate their real significance."

Another important observation made in this case is that the history given by the hyposensitive individual may be totally unreliable. Apparently in the mind of the hyposensitive individual certain symptoms appear of no consequence, and hence the inquiring physician is not informed of their presence. The question which naturally arises in this case is to what extent the psyche may play a rôle in the patient's own reaction to his disease.

The desire to minimize or conceal one's ailments cannot be attributed to hyposensitivity alone. The entire problem of the patient's reaction to his own condition is rapidly being recognized by students of psychosomatic medicine. The psychological mechanisms involved in the production of pain and the emotional make-up of the hyposensitive individual probably play an important rôle in the clinical picture.

It is necessary when taking the history of a hyposensitive person to inquire repeatedly into changes from the usual. Despite the fact that we did do so in this case, it was not until his wife reminded him of what had happened in the past two months that he could recollect at all that he had not been feeling well. Under these circumstances one can realize how unreliable the history of a hyposensitive patient can be when it is taken four or five years after an occlusion, particularly when there had been no pain, but only substitution symptoms.

Various theories have been formulated in an attempt to explain why some cases of coronary occlusion may occur with very mild symptoms, and even without pain. The theory of hyposensitivity of the individual finds most favor. Other factors, such as the state of the collateral circulation may have some importance. Local myocardial damage of an old infarct may also play a rôle in altering the clinical picture. Recently it has been suggested that the symptoms in many cases diagnosed as coronary occlusion may really be due to coronary insufficiency, which would explain the presence of little or no pain. These various theories will be considered briefly.

*Hyposensitivity.* Libman determined the sensitivity of a patient by a simple test which he described as follows:

"One first presses with the thumb of the right hand upon the tip of the mastoid bone (usually the left, unless there be present an inflammatory process in the bone), and then against the styloid process. Pressure against the normal mastoid process causes no pain. Pressure in the direction of the styloid process causes pain in some individuals and not in others. What one really presses upon is a branch of the auricularis magnus nerve . . . . Those who have little or no pain by this test are considered hyposensitive."

Libman further stated that "whereas a mild pain in the sensitive person usually points to a milder form of disease, slight pain in a hyposensitive individual often occurs in the presence of severe conditions."



*Collateral circulation.* The idea that the clinical picture in coronary occlusion may vary according to the state of the coronary arterial circulation of the heart is not a new one. Herrick (20) in 1912 already stated that "the clinical manifestations of coronary obstruction will evidently vary greatly depending on the size, location and number of vessels occluded."

Gross (15) in his classic book on "The Blood Supply to the Heart" was of the impression that the collateral circulation in the heart gradually increased with age. Although this book was chiefly on an anatomical basis, he nevertheless made the observation that coronary occlusion could occur without pain or symptoms. On page 141 of this book there is a roentgenogram of a heart from a female, aged seventy-three, who died of cancer of the gall bladder. According to Gross: "During life she had no symptoms referable to the heart or coronary vessels. In the hospital no signs were found during life indicating a lesion of the heart. Upon injection of the heart at autopsy, however, it was seen that the ramus circumflexus dexter presented to a great extent of its course an arteriosclerotic obliteration which was, in several places, almost complete. The myocardium was absolutely intact, no suggestion of an infarct being present. The case is, in short, very similar to that described by Galli. A more careful observation of the plate shows that a very ample and abundant anastomosis of large, patent rami interventriculares supplied, to a great extent, the right side, and this was further compensated by an extensive labyrinthine felt-work of rami telae adiposae which massively covered the right ventricular surface." . . .

According to Gross: "The conclusions which can be drawn from this case are, that in the seventh decade of life the vascular architecture of the heart is well prepared to receive the brunt of the obliteration even of a main coronary artery, not only on account of the existence of abundant and free anastomoses, but also, as is seen in this case, by the non-negligible factor of the development at this age period of a dense felt-work of arteriae telae adiposae which can compensate and supply considerable blood to the subjacent muscle." . . .

Kugel (23) in 1927 in his description of "An Important Anastomotic Vessel in the Auricle of the Human Heart" made note of the fact that "in several hearts which were the seat of arteriosclerotic coronary disease, this vessel was of unusually large caliber."

Later Gross and Kugel (17) in their study of "The Arterial Blood Vascular Distribution to the Left and Right Ventricles of the Human Heart" found that "gradual development of septal anastomoses serve as a compensatory factor during the latter age periods when sclerotic changes begin to appear," and also that "septal anastomotic vessels play an extraordinarily important rôle in coronary disease where myocardial infarction has taken place."

The observations of Blumgart, Schlesinger and Zoll (5) have added a great deal to our knowledge of the collateral circulation of the heart and its clinical significance. They felt that "regardless of the age of the subject, normal hearts in which there is little or no coronary arteriosclerosis regularly have fine inter-coronary communications, but do not possess an anastomotic circulation through vessels large enough to be functionally significant in obviating the untoward results of rapidly developing coronary narrowing or occlusions." They further



stated that "the development of such anastomoses is not related to age, for they are not present in the hearts of even senile patients when little or no coronary arteriosclerosis is present."

They further stated that "in patients dying with the syndrome of coronary occlusion, i.e., prolonged, crushing chest pain with the signs and symptoms of collapse, the frequent disclosure of a fresh, occluding thrombus or embolus has led to the assumption that thrombosis or embolism of a coronary artery always precipitates these symptoms and signs and that they are produced in no other way. Our observations demonstrate that such is not the case; thrombosis of a coronary artery produces symptoms only if myocardial ischemia follows. When the previous narrowing has been gradual, with concomitant development of an adequate collateral circulation, the final occlusion of the vessel may be asymptomatic, and myocardial necrosis may be entirely absent. Our repeated finding of long-standing complete occlusions, with no history of symptoms and no severe myocardial damage post mortem, is unequivocal."

In collaboration with Dr. Gross (1, 16, 17, 18, 23, 24) on the collateral circulation of the heart, we too came across specimens which showed old occlusions in the coronary arteries, and a study of the hospital charts revealed no clinical history suggesting symptoms of coronary occlusion. However, it was unfortunate that we were not in possession of adequate histories as to existence of cardiac pain prior to death.

In Case 1, which we described in detail, we too felt that we observed a case of coronary occlusion without pain or symptoms. The story was unequivocal. As pointed out already, three physicians on repeated questioning failed to elicit such history, although a statement was suggestive of the occurrence of a coronary occlusion a few years previously. There is evidence that for a few months before he saw us he already had evidence of some myocardial involvement. Even though he may have had a gradual occlusion apparently without pain, he had definite subjective symptoms.

His collateral circulation must have been well-developed, but in addition it must be emphasized that he was also hyposensitive. There is no doubt though that the state of the collateral circulation is a factor in the ultimate clinical picture. It is not impossible then to imagine that some of these cases that have been reported without pain or without symptoms might have been hyposensitives. Although a gradual closure may occur without pain or other subjective symptoms, nevertheless in our experience acute coronary occlusion with myocardial infarction is invariably accompanied by subjective symptoms, even in the absence of pain.

#### LOCAL MYOCARDIAL DAMAGE

It is a well known clinical fact that in cases of angina pectoris the frequency and severity of the attacks of precordial pain are often lessened following an attack of coronary occlusion.

Kennedy (22) in his study of the incidence of myocardial infarction without pain of 200 autopsied cases, found that while only 4 per cent of the attacks of

acute myocardial infarction were painless, an analysis of old attacks from which recovery had occurred showed that about 22 per cent were painless.

The following is a case illustrating this point:—

*Case 2. History:* H. K., a man aged 44 years, on March 8, 1938 had an attack of coronary occlusion and was in bed for four months. At the beginning of the attack he complained of shortness of breath, severe precordial pains with radiation down the left arm, and dizziness. Four months later he had another episode associated with pain in the left shoulder radiating down to his little finger. The electrocardiograms and the clinical course were typical of coronary occlusion. On February 16, 1943 he had an "attack" of sudden dyspnea with collapse. This time he stated that he did not have any pain whatsoever. The electrocardiograms taken at this time and the clinical course were characteristic of acute coronary occlusion. The patient was examined by the Libman method and was found to be moderately hyposensitive.

*Comment.* The question naturally arises why the first and second attacks occurred with pain and the subsequent one without pain. A diseased organ is usually a more sensitized organ, but local myocardial damage may apparently desensitize it to pain.

Some have suggested that the cause of lack of pain is due to the fact that there is not only an infarct but absolute ischemia, while others feel that the lack of pain is due to alteration in the nerve plexuses surrounding the coronary vessels.

Lewis (29) in his observations on pain-sensitive tissues, found "traction on a ligature previously passed around the descending branch of the left coronary promptly calls forth evidence of pain, the dog limping on the left forepaw (Sutton and Lueth). Signs of pain are elicited by such traction, even though the artery remains patent, it therefore seems to come at least in part from tension on the nerves accompanying the artery. Puncturing the heart wall in dogs is said to be painless; the aorta may be punctured painlessly, but signs of pain are sometimes elicited from the adventitia."

The exact mechanism is not clearly understood, how previously existing myocardial damage or a healed infarct serves to disrupt the passage of painful stimuli from the heart. Although local neurogenic factors may be effective in previously damaged hearts in eliminating the pain of myomalacia, the constitutional factor of hyposensitivity may also play a significant rôle in its elimination, as occurred in the last attack of the case we have just presented.

#### CORONARY INSUFFICIENCY

It has been known for some time that acute coronary occlusion may occur without pain post-operatively (3, 35). Recently, however, Master (33, 36) has emphasized the fact that many of these cases of so-called coronary occlusion are really cases of coronary insufficiency. In a recent article he (34) stated: "Coronary insufficiency is due to a sudden inadequacy of coronary blood flow, produced by a number of factors. Thus, unusual effort and emotion increase the work of the heart; acute hemorrhage, shock, tachycardia, heart failure, surgical operations, and aortic valve disease diminish the amount of blood flow through the coronary arteries. If either increased cardiac work or diminished coronary blood

flow develops in the presence of coronary artery disease, the myocardium may become ischemic and, if the precipitating factor persists, necrosis of the heart muscle may ensue. Occasionally no discernible cause of the coronary insufficiency is present.

"Unlike coronary occlusion, pain may be a minor symptom in coronary insufficiency, and sometimes is obscured entirely by the condition causing the ischemia, for example, shock or a surgical operation. Even when present, the pain is often transitory. In other cases status anginosus may be present. In general, when no precipitating factor of an attack is apparent, the differential diagnosis of coronary occlusion and insufficiency may depend on the electrocardiogram."

This clinical classification is of great value if used with the proper sense of balance. One can never be certain whether what might seem to be a coronary insufficiency might not be the prodromal symptoms of an impending acute coronary occlusion of major proportions.

Recently White (49) describing a case of coronary insufficiency, which he called *angina pectoris decubitus* stated that "one cannot over-emphasize the importance of a rest cure during periods of *angina pectoris decubitus*. It is just as important to treat *angina pectoris decubitus* by rest as it is an actual myocardial infarct. It is quite likely that as many deaths have occurred during a period of *angina pectoris decubitus* as during acute myocardial infarction, or even more, owing in part at least to the failure to restrict activities over that period of time."

The clinical picture of coronary insufficiency may resemble that of coronary occlusion, but pain and signs of shock may be absent or inconspicuous. In view of the fact that there may be an absence of pain or shock, it may be of interest to some investigator to determine how many of these people are hyposensitive.

#### DIAGNOSIS OF ACUTE CORONARY OCCLUSION

The diagnosis of acute coronary occlusion with myocardial infarction can only be made after a thorough investigation of the clinical history and subsequent observations of the patient. In coronary occlusion the pain is usually located in the middle of the chest near the sternum. It can be extremely severe and agonizing, and with a tendency to being persistent. In some cases the pain may be referred to the back or to the abdomen. In those cases where the individual is hyposensitive, the pain may be mild or represented by the substitution symptoms of Libman. In rare instances there may be a total absence of pain. In such cases where pain is absent, the presenting symptoms may be sudden dyspnea, sudden increase of myocardial failure, vertigo, syncope, collapse or digestive disturbances. These are observations made a long time ago by Libman.

The pain in acute coronary occlusion is usually not relieved by nitroglycerine. Furthermore the patient may present the picture of shock, with cold and clammy extremities and an ashen gray facies. There is a tendency for the blood pressure to decline and then gradually return towards normal. In some cases the blood pressure remains elevated. Fever and leukocytosis are usually present, but this is absent in an appreciable number of cases. In most instances the increase in

the leukocyte count and the rise in temperature may occur before the sedimentation rate becomes elevated.

In his investigations Bean (4) found that "pericardial friction rubs were heard in 41 per cent with acute pericarditis in coronary occlusion with infarction."

When the opportunity affords, fluoroscopic examination of these patients may reveal a systolic expansion in the area of the left ventricle which is in the region of the infarct.

In addition to all these signs and symptoms, one usually finds elevation of the RS-T segment and a deep Q wave in one or more leads, with progressive change from RS-T elevation to T wave inversion in serial electrocardiograms.

#### DIFFERENTIAL DIAGNOSIS

Severe pain in the chest which may often seem characteristic of acute coronary thrombosis may actually signify other conditions such as pulmonary embolism and pulmonary infarction. In pulmonary embolism and infarction one may get the clinical picture and even electrocardiograms suggestive of acute coronary occlusion.

There are many other conditions which may cause chest pain such as intercostal neuralgia, herpes zoster, fractured rib, and inflammation or disease of the vertebrae, cartilage or fibrous tissue. Visceral disease other than heart affections causing chest pain include lesions of the pleura, diaphragmatic pleurisy, pneumonia, inflammation in the mediastinum, diaphragmatic hernia, etc., etc.

At times certain intra-abdominal conditions such as perforated peptic ulcer and gall bladder disease may closely simulate acute coronary thrombosis with abdominal symptoms.

Another condition which may easily be confused with acute coronary occlusion is acute pancreatitis. Dittler and McGavack reported a case of a 53 year old man who had sharp abdominal pain, nausea, orthopnea and precordial oppression. He was admitted into the hospital in shock. The patient had auricular fibrillation. On admission the blood pressure was 160/90. There was a leukocytosis and the sedimentation rate became elevated. Changes in the electrocardiograms and a subsequent drop in blood pressure to 110/80 made it almost certain that the clinical picture was that of an acute coronary thrombosis. After the patient died, it was found on autopsy that there was necrosis of the pancreas and a peritonitis. Examination of the heart showed that both coronary arteries were patent throughout and on section presented smooth, intact intima.

In their observations, Gottesman, Casten and Beller (53) have pointed out that the electrocardiographic changes which may occur with acute pancreatitis have been repeatedly interpreted as indicating acute coronary occlusion. In experimental work on dogs they induced acute pancreatitis, and on autopsy they found that despite the abnormal electrocardiograms the coronary arteries were normal. They further reported cases of acute pancreatitis where the clinical course and the electrocardiograms which included inversion of the T waves were very suggestive clinically of acute coronary thrombosis. In those instances where they were able to obtain autopsies the coronary arteries were patent.

A case observed by Gottesman, Casten and Beller on the service of Dr. Eli

Moschcowitz was very suggestive of acute coronary thrombosis. The electrocardiograms showed elevation of the RS-T segments in all leads, and the diagnosis of anterior myocardial infarction was made. Death occurred three hours after admission and autopsy revealed an acute fibropurulent pancreatitis. The coronary arteries were patent throughout. They have suggested a "triad for establishing diagnosis of pancreatitis: 1) elevated blood amylase 2) signs of upper abdominal peritoneal irritation and 3) variation from the normal in electrocardiographic tracing which may simulate coronary disease or myocardial infarction."

Clinical and experimental observations have shown that disturbances in the gastro-intestinal tract may be associated with electrocardiographic changes suggestive of coronary disease.

Thus it should be emphasized that there are conditions in the chest or elsewhere which may simulate acute coronary occlusion, and one cannot depend on pain alone, even if associated with electrocardiographic changes, as sufficient basis to make an accurate and final diagnosis of coronary occlusion.

Also one cannot make an accurate diagnosis of coronary disease on electrocardiographic findings alone without obtaining a complete clinical history. Marvin (54) has pointed out that changes in the electrocardiogram particularly the S-T segment and T wave have caused more confusion and trouble than any other portion of the tracings.

There are many conditions, other than coronary atherosclerosis, responsible for abnormalities of S-T segment and T wave. Marvin points out that undoubtedly changes in these segments are found with coronary atherosclerosis but coronary disease is only one of many factors that cause such changes, and it is definitely impossible to decide from the electrocardiogram alone which of these many causes is responsible. "If myocardial infarction is excluded, there is no change in the electrocardiogram that in itself justifies the diagnosis of coronary disease, because the alterations on which this diagnosis is based may be, and often are, due to other causes."

The general impression in the literature is that there is a wide divergence of opinion as to the frequency of acute coronary occlusion and myocardial infarction without pain. Actually this not the case. All those investigators who have carefully defined their criteria as to what they consider pain, and who have included Libman's (30, 31, 32) substitution symptoms as a manifestation of pain, are in complete agreement. Babey (2), Kennedy (22), Pollard and Harvill (39), as well as the writer, interpreted the substitution symptoms of Libman as a manifestation of pain, and under these circumstances it was found that acute coronary occlusion without pain is very rare, at most 4 per cent.

White (48), Levine (27) and Roche (41) who recognized the substitution symptoms as a criteria for pain are also of the opinion that acute coronary occlusion without pain occurs in only about 3 or 4 per cent of the cases.

Others like Barnes (3) report that they have always been skeptical about the occurrence of coronary occlusion without pain, and recently Dressler (10) has stressed that painless attacks are infrequent and that thorough questioning elicits



the fact that there was some kind of anginal pain in the overwhelming majority of cases.

Wolferth (51) states that he has seen only two or three patients with definite electrocardiographic evidence of recent infarction from whom a history of pain or other anginal type of distress could not be elicited.

There are many objections already raised in the literature as to the validity of some of the reports on the high incidence of cases of coronary occlusion without pain. Thus, in order to avoid the pitfalls of incomplete histories, Babey (2) excluded patients who died very suddenly before complete study or those who were too sick to study and died soon after admission. Also he excluded cases of patients who suffered coronary occlusion shortly after operation or when they were under the effects of drugs or anesthesia and whenever the mental state was clouded on admission by uremia or impending coma, and no reliable history was obtainable. Babey (2) also pointed out that almost all reports which declare acute coronary occlusion without pain to be frequent are based on old case records, which can be very misleading. Wolferth (51) has stated that "patients who have suffered a coronary closure weeks or months before may have had such mild pain as to have completely forgotten about it. Questioning all acute cases soon after the attack is the only safe approach. Yet even this is liable to error, for patients occasionally suspect the nature of their attack and deny typical pain out of fear of being told the truth; or their distress may not be classical and be entirely overlooked."

The objections raised by Kennedy (22) are that "most of the previously published reports, which have indicated that painless coronary thrombosis was of fairly frequent occurrence, have failed to take into account the difficulty of obtaining an adequate history under such conditions as sudden death, coma, surgical anesthesia and cerebral vascular accidents. They have also omitted the important distinction between pain and other sensations equally characteristic of coronary disease, such as pressure, constriction, and burning."

Similar criticisms have also been raised by Pollard and Harvill (39), who stated that "some authors have included in the painless group all cases in which the patient did not use the term pain in describing his symptoms, even though 'precordial discomfort', 'precordial distress' or 'a sense of constriction in the chest' did occur. Some authors have included in the painless group cases in which the patient had experienced transient anginal pain of the type which occurs in angina of effort, but no prolonged myocardial damage or failure."

The problem of the personal interpretation of pain is not a simple one as has already been pointed out by Lewis (29) who stated that "it must be obvious to anyone who has given thought to the matter that most descriptions of pains—as these are supplied to us by those who suffer from such pains in words purely of their own choice—fail to convey sufficiently precise ideas of the sensations experienced and therefore do not adequately identify the pains. One reason for inaccuracy and inadequacy of description is the difficulty of calling up exact memories of what has been felt some time previously. It is certain that the closer the description is to the event the more accurate it becomes, and that the

description is most accurate when given at the time pain occurs and deliberately revised at the time the pain recurs. Another reason is the difficulty of finding right words of description and apposite illustrations; to do this requires observational and didactic skill in a degree which few possess . . . ."

Unless the examining physician is clear in his own mind as to what is pain, and unless he is acquainted with the importance of the substitution symptoms as described by Libman, he is apt to make a serious error in diagnosis. The following case report is an example:—

*Case 3. History:* R. K., a young man of 28 years of age, who had been in Officers' Candidate School in Miami Beach, was brought in by his father on Sunday, September 13, 1942 for examination. For the past week he had felt a constriction around the head associated with weakness in the arms after marching, walking and dancing, and with it he felt quite weak. He also noticed that after meals or walking, he would have a constricting sensation around the chest. He had been examined by an Army officer who made a diagnosis of neuro-circulatory asthenia and salt deficiency.

*Examination:* His heart was normal in size, shape and position. His blood pressure was 110 systolic and 80 diastolic and pulse rate, 78. Electrocardiograms showed a cove plane inversion of  $T_2$  and  $T_3$  with prominent Q waves in leads II and III. He was hyposensitive when examined by the styloid pressure test of Libman. It was three days before graduation, and the father was informed that it would be a great risk to have this boy march or drill any further even though it meant that he would not obtain his commission. He was admitted to the Army hospital where the diagnosis of coronary occlusion was confirmed by the cardiologist. After six weeks in bed he made a complete recovery, and was subsequently honorably discharged from the Army.

*Comment.* The incidence of coronary disease in youth has already been described by Glendy, Levine and White (13), and its importance in the armed services is being recognized as indicated by the work reported by French and Dock (12) on "Fatal Coronary Arteriosclerosis in Young Soldiers."

Had this soldier with acute coronary occlusion and mild substitution symptoms been allowed to march, the outcome could easily have been fatal. It cannot be over-emphasized that one should treat with great caution those hyposensitive individuals with acute coronary occlusion with mild substitution symptoms. It is in this group where errors in diagnosis are most apt to be made, and the serious nature of the underlying illness is most apt to be overlooked by the physician and the patient.

#### SUMMARY AND CONCLUSIONS

In a study of 350 cases of coronary occlusion only ten were found to be without pain, an incidence of less than 3 per cent. A review of the literature on this subject reveals that all those investigators who clearly define their criteria for pain, and who have considered Libman's substitution symptoms as a manifestation of pain, also found a very low percentage without pain.

Although severe precordial pain of a characteristic nature may occur in coronary occlusion, it should be emphasized that there are many cases where the symptoms are atypical, the pain mild, or in rare cases, even absent. In the hyposensitive individual pain may be manifested by substitution symptoms, or when

pain is absent, the presenting symptoms may be a sudden dyspnea, sudden increase in myocardial failure, vertigo, syncope, digestive disturbances or collapse.

It is in the hyposensitive individual that one is most apt to overlook the seriousness of the underlying condition. One cannot depend on pain alone, even associated with the electrocardiograms which might seem to be characteristic, for the final diagnosis of acute coronary occlusion. One must go into the history in great detail and consider the entire clinical picture.

#### BIBLIOGRAPHY

1. ANTOPOL, W., AND KUGEL, M. A.: Anomalous Origin of the Left Circumflex Coronary Artery, *Am. Heart J.* 8: 802, 1933.
2. BABEY, A. M.: Painless Acute Infarction of the Heart, *New England J. Med.* 220: 410, 1939.
3. BARNES, A. R.: Acute Coronary Occlusion Without the Characteristic History of Anginal Pain; Course, Treatment and Electrocardiographic Findings, *M. Clin. North America*, 18: 477, 1934.
4. BEAN, W. B.: Infarction of the Heart; Symptomatology of Acute Attack, *Ann. Int. Med.* 11: 2086, 1938.
5. BLUMGART, H. L., SCHLESINGER, M. J., AND DAVIS, D.: Studies on the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis, and Myocardial Infarction to the Pathologic Findings, with Particular Reference to the Significance of the Collateral Circulation, *Am. Heart J.* 19: 67, 1940.
6. BOYD, L. J., AND WERBLOW, S. C.: Coronary Thrombosis with Pain, *Am. J. M. Sc.* 194: 814, 1937.
7. BREUNN, H. G., TURNER, K. B., AND LEVY, R. L.: Notes on Cardiac Pain and Coronary Disease, *Am. Heart J.* 11: 34, 1936.
8. DAVIS, N. S.: Coronary Thrombosis without Pain; Its Incidence and Pathology, *J. A. M. A.* 98: 1806, 1932.
9. DAVIS, N. S.: Cardiac Infarction without History of Pain, *M. Clin. North America* 16: 315, 1932.
10. DRESSLER, W.: Myocardial Infarction Indicated by Angina Pectoris of Effect or by Brief Attacks of Angina of Rest, with Remarks on Premonitory Pain, *Am. Heart J.* 28: 81, 1944.
11. EDEIKEN, J. AND WOLFERTH, C. C.: Persistent Pain in the Shoulder Region Following Myocardial Infarction, *Am. J. M. Sc.* 191: 201, 1936.
12. FRENCH, A. J., AND DOCK, W.: Fatal Coronary Arteriosclerosis in Young Soldiers, *J. A. M. A.* 124: 1233, 1944.
13. GLENDY, E. E., LEVINE, S. A., AND WHITE, P. D.: Coronary Disease in Youth, *J. A. M. A.* 109: 1775, 1937.
14. GORHAM, L. W., AND MARTIN, S. W.: Coronary Occlusion Without Pain, *Arch. Int. Med.* 62: 821, 1938.
15. GROSS, L.: *The Blood Supply to the Heart*, New York, Paul B. Hoeber, Inc., 1921.
16. GROSS, L., EPSTEIN, E. Z., AND KUGEL, M. A.: Histology of the Coronary Arteries and their Branches in the Human Heart, *Am. J. Path.* 10: 253, 1934.
17. GROSS, L., AND KUGEL, M. A.: The Arterial Blood Vascular Distribution to the Left and Right Ventricles of the Human Heart, *Am. Heart J.* 9: 165, 1933.
18. GROSS, L., KUGEL, M. A., AND EPSTEIN, E. Z.: Lesions of the Coronary Arteries and their Branches in Rheumatic Fever, *Am. J. Path.* 11: 253, 1935.
19. HEBERDEN, W.: An Introduction to the Study of Physic: Some Account of a Disorder of the Breast—Read at the College, July 21, 1768—Reprinted from *Medical Transactions*, 2: 59-67, 1786—New York, Paul B. Hoeber, Inc., 1929.

20. HERRICK, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries J. A. M. A. 59: 2015, 1912.
21. HOFFMAN, M. H.: Significance of the Sedimentation Rate in Coronary Occlusion, Minnesota Med. 19: 512, 1936.
22. KENNEDY, J. A.: The Incidence of Myocardial Infarction Without Pain in 200 Autopsied Cases, Am. Heart J. 14: 703, 1937.
23. KUGEL, M. A.: An Important Anastomotic Vessel in the Auricle of the Human Heart, Proc. New York Path. Soc. p. 98, 1927.
24. KUGEL, M. A.: Anatomic Studies on the Coronary Arteries and their Branches, Am. Heart J. 3: 260, 1928.
25. KUGEL, M. A. AND LICHTMAN, S. S.: Factors Causing Clinical Jaundice in Heart Disease, J. A. M. A. 52: 16, 1933.
26. LAUFER, S. T.: Subacute Myocardial Infarction or Necrosis, Canad. M. A. J. 45: 236, 1941.
27. LEVINE, S. A.: personal communication.
28. LEVINE, S. A., AND ROSENBAUM, FRANCIS F.: Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction, Arch. Int. Med. 68: 913 and 1215, 1941.
29. LEWIS, SIR THOMAS: Pain, New York, The MacMillan Co., 1942.
30. LIBMAN, E.: Some Observations on Thrombosis of the Coronary Arteries, Tr. A. Am. Phys. 34: 138, 1919.
31. LIBMAN, E.: Observations on Sensitiveness to Pain, Tr. Assoc. Am. Phys. 41: 305, 1926.
32. LIBMAN, E.: Studies in Pain, Tr. Assoc. Am. Phys. 44: 52, 1929.
33. MASTER, A. M.: personal communication.
34. MASTER, A. M., CARROLL, H. H., AND ANDREWS, C.: Coronary Insufficiency and Coronary Occlusion, U. S. Nav. M. Bull. 40: 810, 1942.
35. MASTER, A. M., DACK, S., AND JAFFE, H. L.: Post-Operative Coronary Thrombosis, J. A. M. A. 110: 1415, 1938.
36. MASTER, A. M., JAFFE, H. L., AND DACK, S.: Coronary Occlusion, Coronary Insufficiency and Angina Pectoris: A Clinical and Post-Mortem Study, Am. Heart J. 27: 803, 1944.
37. MORAWITZ AND HOSCHREIN quoted by William D. Stroud and Joseph A. Wagner.
38. MOSCHOWITZ, E.: Vascular Sclerosis with Special Reference to Arteriosclerosis, New York, Oxford University Press, 1942.
39. POLLARD, M. H. AND HARVILL, T. H.: Painless Myocardial Infarction, Am. J. M. Sc. 199: 628, 1940.
40. RICHTER, H. A.: Acute Coronary Occlusion: Points on Diagnosis and Treatment, Illinois M. J. 70: 278, 1936.
41. ROCHE, C. F.: personal communication.
42. SAPHIR, O., PRIEST, W. S., HAMBURGER, W. W., AND KATZ, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis, and the Resulting Myocardial Changes, Am. Heart J. 10: 567 and 762, 1935.
43. SIGLER, L. H.: The Electrocardiogram, New York, Grune and Stratton, 1944.
44. SMITH, H. L. AND BRINK, J. R.: Acute Coronary Thrombosis Without Characteristic Pain and Without Symptoms of Shock: Report of Three Cases, Minnesota Med. 19: 346, 1936.
45. STRONG, C. F.: Cardiac Pain, Canad. M. A. J. 48: 318, 1943.
46. STROUD, W. D. AND WAGNER, J. A.: Silent or Atypical Coronary Occlusion, Ann. Int. Med. 15: 25, 1941.
47. WEARN, J. T.: Thrombosis of the Coronary Arteries, Am. J. M. Sc. 165: 250, 1923.
48. WHITE, P. D.: personal communication.
49. WHITE, P. D.: Seven Common and Important Problems in the Management of Heart Diseases and Disorders, Med. Clin. North America 1129, 1944.
50. WHITE, S. M.: Non-Painful Features of Coronary Occlusion, Ann. Int. Med. 8: 690, 1934.

51. WOLFERTH, C. C.: Present Concepts of Acute Coronary Occlusion, J. A. M. A. 109: 1769, 1937.
52. DITTLER, EDGAR LEON, AND MCGAVACK, THOMAS H.: Pancreatic Necrosis Associated with Auricular Fibrillation and Flutter, Am. Heart J. 16: 354, 1938.
53. GOTTESMAN, JULIUS, CASTEN, DAVID, AND BELLER, ABRAHAM J.: Changes in the Electrocardiogram Induced by Acute Pancreatitis, J. A. M. A. 123: 893, 1943.
54. MARVIN, H. M.: Diagnosis of Coronary Artery Disease, New Eng. J. Med. 226: 251-254, 1942.



## ACUTE TOXIC NEPHROSIS IN CARBON TETRACHLORIDE POISONING<sup>1</sup>

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According to Smetana (1) the diagnosis of carbon tetrachloride poisoning presents no difficulty if one is familiar with the toxic manifestations, particularly renal; the clinical symptoms and laboratory findings are so characteristic and uniform as to lead to the correct diagnosis without adequate history. That there is a lack of familiarity with the injurious effects of carbon tetrachloride, their prevention, diagnosis, clinical manifestations and treatment, is evidenced by mounting reports of poisoning (2). Wartime use of this degreasing solvent emphasizes the problem. This case report of severe acute renal insufficiency with full recovery illustrates and reviews that newer knowledge of carbon tetrachloride poisoning.

### CASE REPORT

*History:* This 22 year old soldier was in a detail of fifteen men assigned to degreasing guns with carbon tetrachloride after a preliminary cleansing with common gasoline (73 octane). His exposure was intermittent, totalling about five hours on the 3rd, and seven hours on the 4th of December. The detail worked in a large, stove-heated room in which two windows and a door were kept open. He sat with most of the others at a long bench which held a deep tray containing 1-2 quarts of carbon tetrachloride washing gun parts that had been cleaned with gasoline contained in another tray on this bench. Nine of the fifteen soldiers became acutely ill in the late evening of the second day with headache, nausea, vomiting and backache. One soldier went rapidly into such a shock-like state that it was feared he was about to die; he and seven others recovered fully within 48 hours, whereas this patient progressed to renal insufficiency. One of the acutely ill men handled neither gasoline nor carbon tetrachloride. Although the route was predominately by inhalation, some of the carbon tetrachloride may have been absorbed through the skin and perhaps ingested.

The past history disclosed no significant illnesses but did reveal that for several years the patient was accustomed to consuming large quantities of hard liquor, as much as a quart and a half daily. However, he at first maintained that for the past year he had "sworn off"; closer questioning revealed that on the evening prior to the first exposure he consumed 25 or 30 beers and "only two whiskeys." About three nights a week he "swore off" in this manner. Curiously, and perhaps significantly, he consumed much milk, drinking 6 to 8 glasses a day regularly.

*Course:* The course of the illness can be divided into the following phases: latent, acute toxic, delayed, renal insufficiency and recovery.

Shortly after completing his second afternoon of work, the patient had malaise, loss of appetite and drowsiness. He omitted supper and went to sleep. Five hours later he awoke acutely ill, nauseated, began to vomit, was quite dizzy and weak, and was hospitalized with the additional complaints of backache, and pains radiating down the back of the legs. The temperature was 102°F, pulse 128, and respirations 24. He was treated with morphine, glucose and saline, atropine and repeated intravenous injections of calcium.

On the second day of illness there seemed to be some improvement, although nausea and vomiting were persistent and a cloudy mental state prevailed and persisted for the next nine

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<sup>1</sup> From the Medical Service of Lt. Col. Marshall N. Fulton, MC, Valley Forge General Hospital, Colonel Henry Beeuwkes, MC, Commanding.

days. The temperature was 99.8°F and thereafter became normal. He received 10 cc. of 10 per cent calcium gluconate intravenously and 40 grains of calcium gluconate orally.

On the third day the clinical condition suddenly became worse with exacerbation of the dizziness, nausea and vomiting. This was accompanied by distension and abdominal pain, generalized as well as localized in the right upper quadrant. Oliguria, previously attributed to dehydration, failed to respond to 3,000 cc. of intravenous 10 per cent glucose.

There was no improvement on the fourth day despite repeated intravenous infusions, calcium gluconate and intramuscular thiamine. He was then transferred to Valley Forge General Hospital for diagnosis and treatment.

*Examination:* The patient was an apathetic, nauseated, drowsy soldier, temperature 98.2°F, pulse 64, respirations 24. The eyes were puffy, the sclerae subicteric and a urinous odor was detectable in his breath. There was slight bleeding from the right nostril. There was moderate stomatitis and the right tonsil was ulcerated. Heart and lungs were negative. The abdomen was distended, the liver edge palpable one to two fingerbreadths below the costal border and quite tender. Spleen and kidneys were not palpable, but there was slight costo-vertebral tenderness. Deep reflexes were normal; a few muscular twitches were noted, but no Chvostek. Treatment was begun by restriction of all oral intake. Fifty per cent glucose, repeated calcium gluconate and 5 per cent glucose alternately in saline and distilled water were given intravenously.

Laboratory determinations<sup>2</sup> (Tables 1 and 2) corroborated the clinical impression of predominant renal insufficiency. On the fifth day, although vomiting was slight but bloody, the general condition was worse. The symptoms persisted and the abdominal complaints increased. The puffiness was a little more marked. Three hundred cc. of plasma were given in addition to intravenous glucose in saline and in distilled water, a total intake of 3,720 cc. Several injections of caffeine sodium benzoate were also given. The condition was unchanged the following day except that vomiting ceased. The lungs were clear, the second pulmonic sound was accentuated and reduplicated. There was puffiness of the face and skin but no pitting edema. Treatment continued as previously indicated.

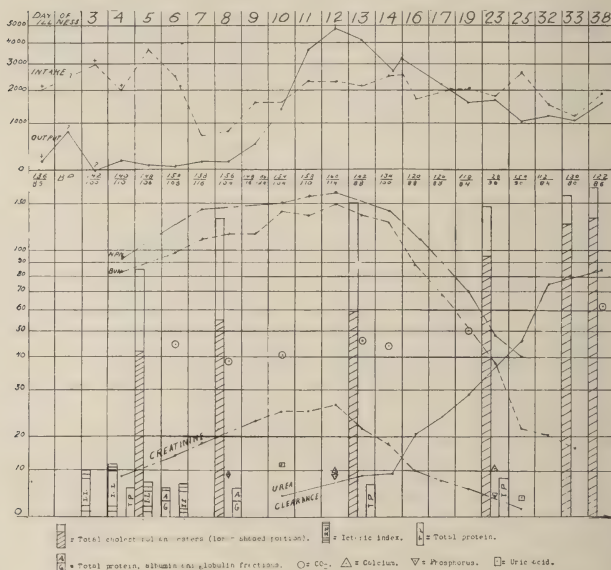
On the seventh day the condition appeared critical. Headache was prominent and the breath strongly uremic. He vomited a total of 180 cc. of frankly bloody material. Abdominal pain was severe, the liver edge being enlarged to the umbilicus and markedly tender. A superficial scratch of the neck resulted in bleeding so profuse as to require compression. There was also a very brisk epistaxis following picking of the nose. Vitamin K (1 cc. Hykinone) daily was administered and continued for seven days. Manifestations of a hemorrhagic diathesis were not noted after the ninth day. Intramuscular thiamine, 50 mg. daily, previously administered at intervals, was given daily for seventeen days. In view of the imminent congestive failure all intravenous fluids were discontinued and the patient allowed only an irreducible minimum of fluids. The patient felt better on the eighth day despite the appearance of rales in the chest and peripheral edema. Another brisk epistaxis occurred. There was cough with expectoration of thick, bloody mucopurulent sputum. X-ray of the chest disclosed early pulmonary congestion, patches of broncho-pneumonia and borderline cardiac enlargement. On the ninth day there was frank congestive failure with numerous rales at both bases, probable ascites, liver edge was tender and at the umbilicus, and there was pitting edema of the abdominal wall and lower extremities. There were signs of increased neuro-muscular irritability. There was also an alarming episode of 45 minutes duration in which there was confusion, severe headache, mild convulsion, progressive impairment of vision resulting in complete blindness. The blood pressure, previously elevated (Table 1), rose to 186 systolic and 124 diastolic at this time. X-ray disclosed remarkable cardiac enlargement, pulmonary edema, broncho-pneumonia, and a small effusion at the right base. The patient was able to retain 1½ grams of sodium bicarbonate and vitamin capsules containing 30,000 units of vitamin A and 3,000 units of

<sup>2</sup> Grateful acknowledgment is made to the Laboratory Staff, Lt. Edmund P. Finch and Captain Hans Schlumberger, for their enthusiastic cooperation.

vitamin D. For the next three days he received 3 grams or slightly more of sodium bicarbonate and for the next three weeks about 100,000 units of vitamin A and 10,000 units of vitamin D daily.

The condition on the tenth day was generally the same. An encouraging urinary output of 1,419 cc. was charted. From the eleventh through the eighteenth day there was a striking diuresis of nearly 26 liters. Within 48 hours there were only traces of the water reten-

TABLE 1  
*Composite of intake, output, blood pressure and blood chemistry*



Observations charted on semi-logarithmic paper. Non-protein nitrogen, blood urea nitrogen, cholesterol and cholesterol esters, creatinine, calcium, phosphorus and uric acid recorded in milligrams per cent. Icteric index in conventional units. Total protein in grams per cent. CO<sub>2</sub> in volumes per cent. Urea clearance in per cent of average normal function.

tion. The mental symptoms rapidly disappeared. Expectoration of bloody sputum, about an ounce daily, continued through the thirteenth day. X-ray on the sixteenth day revealed a normal heart and clearing of the pneumonia and edema. The appetite returned rapidly and by the fourteenth day it was possible to institute a diet of 2,500 calories with 450 grams of carbohydrate, 50 grams of protein, and 20 grams of fat. After four days the protein was increased to 75 grams and the fat to 40 grams. From the twenty-third day the patient was able to tolerate protein of 90 grams and fat of 60 grams. Clinical improvement

TABLE 2  
*Composite of urine and blood findings*

| DAY OF ILLNESS | 1 | 2    | 3 | 4 | 5 | 7 | 8 | 9 | 10 | 11 | 13 | 14 | 15 | 16 | 17 | 18 | 20 | 24 | 25 | 33 | 38 |
|----------------|---|------|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Urine          |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Sp. Gr.        |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Alb.           |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Epith.         |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| WBC            |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| RBC            |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Casts          |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Lead           |   | 0.33 |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Blood          |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| RBC            |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| HGB            |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| WBC            |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Platelet       |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Hemat.         |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Sed Rate       |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Prothrom.      |   |      |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |

\* Specific gravity, where underlined, indicates maximum specific gravity of concentration test. Sediment is charted in units per high power field of centrifuged specimen. Lead is recorded as milligrams per liter urine.

Red blood cells in millions. Platelets in thousands, numerator result obtained in patient, denominator obtained in normal control. Prothrombin time in seconds, numerator obtained in patient, denominator in normal control.

Misc., bleeding time—8 min. (7th day); bromsulfalein retention—0 (38th day).

was rapid and all evidences of liver and renal damage had disappeared at the time of return to full duty after forty-five days of hospitalization that included a sick furlough. (The final urea clearance of 89 per cent of average normal function is not charted.)

*Laboratory Data:* Table 1 details the outstanding features. In addition to the progressive retention of nitrogenous products there is also elevation of phosphorous and uric acid. The creatinine levels are striking, reaching a peak elevation of 26.4. The peak of retention was reached about thirty-six hours after diuresis had started. Three weeks elapsed between the peak levels and the return to normal, the return being inversely proportional to the urea clearance. The earliest determination of the latter, on the tenth day, was 4 per cent of average normal. The icteric index was never higher than 11.5 and normal from the fifth day on. The total protein was initially reduced with a minimum of 5.2 grams but without reversal of the A/G ratio. Total cholesterol was strikingly depressed to 86 with esters of 42; these remained low for several weeks, becoming normal on the thirty-second day. Whole blood chlorides were 430 on the fourth, sixth and seventh days; plasma chlorides were 600 mg. per cent on the sixteenth day and 640 on the twenty-fourth day. Low specific gravity of the urine and tendency to fixation despite oliguria were noted. Albuminuria was not massive. Microscopic hematuria and prolonged pyuria were present, but the paucity of epithelial cells and casts is noteworthy. The initial lead determination indicates a marked exposure, the second determination a moderate exposure and the final finding approaches normal values. Red cells and hemoglobin were not significantly affected except for a possible early hemoconcentration. An initial leukocytosis and polynucleosis were followed by normal or mildly elevated values. The platelets were significantly depressed, remaining so for twenty-five days at least. The prothrombin time was mildly elevated for a short period. There was no retention of bromsulfalein on the thirty-eighth day (Table 2).

#### COMMENT

Poisoning from carbon tetrachloride frequently results in a clinical picture in which kidney damage is predominant. Of 141 collected cases of poisoning (1), 33 (23 per cent) had kidney damage. The inhalation route favors renal involvement; 75 per cent of the instances of renal insufficiency developed after inhalation. Experimental poisoning has revealed that the concentration of carbon tetrachloride after ingestion is greater in the portal circulation than in the general circulation, whereas after inhalation the concentration reaching the liver and kidneys is about equal.

The influence of alcoholism on kidney susceptibility is impressive. Carbon tetrachloride is said to be more toxic to the kidney when liver function is abnormal, as in hepatic cirrhosis. Smetana (1) reported three cases of poisoning; the two fatalities were in alcoholics. The co-worker of one of his fatal cases, a teetotaler, worked in the same room for the same length of time and although he was affected with headache and gastro-intestinal distress, he recovered quickly. Perry (2), reporting 88 cases of carbon tetrachloride poisoning, five of whom required hospitalization, described two fatal cases in individuals who were heavy periodic drinkers. Autopsy revealed "acute nephritis" in both instances. The three other cases with dominant features of severe gastro-intestinal upset and renal damage recovered in spite of severe illness. The factor of alcoholism is noted in this case report but was possibly counteracted to some extent by the large daily consumption of calcium. Animal experiments indicate that the previous diet, particularly the calcium content, is important. Length and mode of exposure and alcoholism are not the sole factors; individual susceptibility is also



important. Ashe and Sailer (3) attribute the fatal uremia in their report to individual susceptibility. Smith (4) reports an instructive instance in a female employed in a jewelry cleaning establishment. Some of her co-workers developed an acute but brief poisoning; one girl who dipped the jewelry in the solvent was unaffected, yet the patient who did not handle the solvent contracted severe kidney damage with eventual recovery. Exact knowledge of the amount of exposure of each of the soldiers was impossible, but review of the conditions under which the detail worked failed to explain why six of them escaped unscathed.

Liver damage in this case was evident from laboratory examination but might easily have been overlooked clinically. There was brief slight icterus and a slightly enlarged tender liver. The subsequent enlargement of the liver reflected water retention and congestive failure, neither of which seemed to impair liver function further. The cholesterol and ester depression were laboratory indications of prolonged liver damage. Fasting blood sugars were normal. Vitamin K metabolism was only mildly impaired.

Hemorrhagic tendency is common in carbon tetrachloride poisoning. It results probably from several factors. Fibrinogen, not estimated in this instance, may be reduced (liver damage). Prothrombin may also be reduced, but in our studies the prothrombin time approached normal at a period when the patient had significant bleeding with a bleeding time of 8 minutes. Another factor is the prolonged reduction in platelets. A toxic capillary factor is also probable.

#### DISCUSSION

The clinical aspects of carbon tetrachloride poisoning are characteristic (1). The initial symptoms are headache, dizziness, general malaise, fever, and sometimes irritation of the nose and eyes. Soon thereafter, there is gastro-intestinal irritation manifested by nausea, vomiting, diarrhea and not infrequently hematemesis; jaundice sets in and may be severe. After several days, during which the gastro-intestinal symptoms remain more or less stationary and the jaundice increases, there develop clinical signs of renal involvement, such as oliguria, sometimes anuria, epileptiform convulsions, hypertension and generalized edema; cyanosis and pulmonary edema may develop and uremic coma is not rare. Hemorrhagic diathesis is common.

The anatomical basis for the renal symptoms is essentially a "nephrosis" characterized by distension of the spaces of Bowman with an albuminous precipitate, swelling of the lining cells, swelling and vacuolation of cells of the proximal convoluted tubules, degeneration and necrosis of distal convoluted and Henle loops with plugging of the lumens and granular, hyaline and cellular casts in the tubules. Destruction of the basement membrane and interstitial involvement are minimal.

Clinically and pathologically then, the renal lesion of carbon tetrachloride poisoning offers a good prognosis provided the patient reaches the recovery stage. There is reported (4) an instance of acute toxic renal insufficiency as a result of

inhalation of carbon tetrachloride with predominant features of vomiting, anuria and hematuria. This 56 year old man recovered completely and died ten months later of an unrelated condition. At autopsy the kidneys were pronounced normal for a man of that age and the liver showed no abnormality. Corcoran, Taylor and Page (5) report a case of renal injury resulting from inhalation. In their case the urea nitrogen rose to 75.3 mg. per cent and the urea clearance was 5 per cent of normal. Their detailed studies of renal function led to the conclusion that there was "convincing evidence of renal restitution to integrity." In this case report the clinical and laboratory data indicate renal damage of maximum severity compatible with recovery. Creatinine retention, usually considered prognostic of fatal outcome if approaching 10 mg. per cent, reached the exceptional value of 26.4 mg. per cent. That complete recovery ensued is encouraging not only for similar instances but for the various allied toxic nephroses. (Although full return of urine concentrating power had not occurred at time of discharge, it can be expected in the presence of a normal urea clearance that such recovery will take place within several months.) The exact role of lead absorption could not be evaluated. It may have contributed to the toxicity, particularly the mental state, but all the significant symptoms and findings in this case have been described in other reports of carbon tetrachloride poisoning.

#### TREATMENT

Prevention of accidental poisoning should be the primary approach. Increasing reports of poisoning indicate the lack of universal familiarity with the toxicity of carbon tetrachloride. In this connection it is to be emphasized that the generally accepted figure of allowable concentration of carbon tetrachloride is four times too high (6). In an editorial (2) appended to Captain Perry's report, the dangers connected with the use of solvents were re-emphasized, attention was again directed to Ordnance Safety Bulletin No. 8 (April 21, 1941) and it was insisted that medical officers familiarize themselves with the types and chemical constituents of solvents used by troops. The factor of individual susceptibility also deserves attention and consideration.

Liver and kidney damage should be immediately presumed in every instance of poisoning. There should be no expectant period of a day or two in the hope that the patient will recover promptly (as many will). The phase of delayed effects merges so indistinguishably with the phase of severe renal or hepatic damage that treatment must be instituted promptly. Where the early manifestations are those of shock, transfusion or plasma are indicated. Since vomiting is a prominent feature and the resulting dehydration obscures or complicates concomitant renal disease, fluids should be given promptly and parenterally. It is of utmost importance to attempt to promote and maintain urinary output. The regulation of intake and the management of renal complications necessitate careful recording of intake and output. The aim is to keep the urinary output at about 1,500 cc. daily, but if the output declines extreme care must be exercised not to "drown the patient in his own fluids." Despite such precautions heart failure and pulmonary edema may develop (3). Ten per cent glucose intravenously is

the conventional solution employed, but whether in saline, Ringer's solution, or in distilled water depends on the state of hydration and laboratory determinations. Further protection of the liver is afforded by 50 per cent glucose intravenously. Where glucose is used, thiamin chloride is theoretically indicated.

Experimental evidence, favored by the clinical impression in this case, points to the value of repeated intravenous calcium (10 cc. of 10 per cent calcium gluconate, several times daily). Minot and Cutler (7) have shown that guanidine accumulates after liver damage. Calcium detoxifies guanidine in an unknown manner. Not only can calcium protect against lethal doses of guanidine but it can also protect markedly an animal with extensive liver damage against carbon tetrachloride poisoning. Hemorrhagic tendency can be combatted by parenteral vitamin K and transfusions. High carbohydrate diet in the recovery phase, with high protein as soon as tolerated, not only combats liver damage but aids in the rapid restoration to total normalcy.

#### SUMMARY

1. A case of acute severe renal insufficiency resulting from inhalation (mainly) of carbon tetrachloride is detailed. The salient features were a history of alcoholism, mental symptoms, acute toxic manifestations, gastro-intestinal irritation, indications of mild hepatic damage, hemorrhagic diathesis, oliguria, azotemia, hypertension, hypertensive encephalopathy, broncho-pneumonia, anasarca of combined renal and cardiac origin, and uremia. Full clinical recovery occurred without any permanent kidney or liver damage.

2. The pertinent laboratory data are recorded.

3. The prevention, diagnosis, clinical manifestations, treatment and prognosis of carbon tetrachloride poisoning are discussed.

#### BIBLIOGRAPHY

1. SMETANA, HANS: Nephrosis Due to Carbon Tetrachloride, *Arch. Int. Med.*, 63: 760, 1939.
2. PERRY, WILLIAM J.: Carbon Tetrachloride Poisoning: A Report of Eighty-eight Cases (With an S.G.O. Note). *Army Med. Bull.*, No. 64: 70, 1942.
3. ASHE, WILLIAM F., AND SAILER, SEATON: Fatal Uremia Following Single Exposure to Carbon Tetrachloride Fumes. *Ohio State M. J.*, 38: 553, 1942.
4. SMITH, ADELAIDE R.: Acute Nephritis From Exposure to Carbon Tetrachloride. *Indust. Hyg. Bull.*, 22: 171, 1943.
5. CORCORAN, A. C., TAYLOR, R. D., AND PAGE, IRVINE H.: Acute Toxic Nephrosis. A Clinical and Laboratory Study Based on a Case of Carbon Tetrachloride Poisoning. *J. A. M. A.*, 123: 81, 1943.
6. ELKINS, H. B.: Maximal Allowable Concentrations I. Carbon Tetrachloride. *J. Indust. Hyg. & Toxicol.*, 24: 233, 1942.
7. GOODMAN, L., AND GILMAN, A.: *The Pharmacological Basis of Therapeutics*. New York, The Macmillan Company, 1943, pp. 888.

## THE CONTEMPORARY TREATMENT OF CHRONIC SIMPLE GLAUCOMA<sup>1</sup>

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The term "glaucoma" may be loosely applied to any ocular syndrome characterized by an abnormal rise of pressure within the eye. In this discussion, we shall only consider the therapy of the most common form of ocular hypertension, namely, chronic simple glaucoma. The pathogenesis of this disease is unknown and its course is characterized by an insidious loss of vision and visual fields. Unless therapeutically arrested, blindness is the almost inevitable consequence. The importance of this malady is indicated by the fact that it produces approximately 10 per cent of all blindness in the United States (1).

We shall not consider the acute congestive type of glaucoma, which generally responds well to surgery, nor the secondary type of glaucoma, caused by antecedent ocular disease. As a matter of fact, in the latter variety, where the elevation of tension is produced by other disease processes, the treatment may be altogether at variance with that for the chronic simple type.

Since the basic nature of chronic simple glaucoma is obscure, the treatment of the disease is still completely empirical. A constant challenge is thus presented by this disease to those ophthalmologists who yearn for a more rational approach to therapy, although fair success has been obtained through contemporary medical and surgical means. The present treatment of chronic simple glaucoma involves three possible approaches: first, the general care of the patient, including psychotherapy of which we shall speak more fully later; second, local medical treatment of the eye; and third, surgery. The response to treatment of an eye with chronic simple glaucoma is unpredictable and subject to variations over a period of time. The efficacy of any form of therapy, therefore, must be evaluated at frequent intervals by careful tests of those visual functions which are insidiously and irreversibly impaired when the disease is inadequately controlled. The state of visual acuity, ocular tension, peripheral and central fields, and the appearance of the fundus are important factors in determining the status of the glaucomatous eye, and the adequacy of its treatment.

Ophthalmologists generally agree that the majority of cases of chronic simple glaucoma eventually require surgery, and it has been proven beyond a doubt that one of the greatest therapeutic mistakes is to delay an operation after the indications for it have become apparent. However, since intraocular surgery involves certain serious hazards, it is advisable first to try to control the disease by medical means. The success of such an attempt must be determined at intervals by the functional tests mentioned, and should not be continued beyond a reasonable time, the length of which depends upon the severity and tempo of the pathological process.

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## GENERAL MEDICAL CARE

The least fruitful approach to the treatment of chronic simple glaucoma has been the general medical care of the patient. No definite mechanism whereby the state of general bodily health affects the local ocular disease has been established, although many investigations have been conducted to prove such a relationship. The oft repeated statement of Lagrange that glaucoma represents a "sick eye in a sick body" may very well be true, but the exact nature of the general disturbance has unfortunately not been determined. Nevertheless, general hygienic measures are usually advocated as an early step in the treatment of this disease. In a set of rules for patients with glaucoma formulated by the Committee on Glaucoma of the National Society for the Prevention of Blindness, there are several suggestions relating to general hygiene (2). However, a too rigid control of the patient's life and habits has been found to encourage a tense hypochondriacal attitude which may increase an already pre-existing anxiety.

Mention should be made of two specific methods recommended in recent years to control glaucoma by systemic treatment. The first was suggested by Josephson (3) in 1935, who claimed good results with the use of adrenal cortical extract; and the second by Miller (4) in 1939 and by Alvis (5) in 1940, both of whom used a splenic extract. The good results claimed for these agents have not been confirmed.

The possibility of an extra-ocular origin of glaucoma has been widely discussed. Elwyn (6) and others have suggested that the basic dysfunction may be a derangement of a central autonomic regulatory control of intraocular pressure. However, no definite proof for such an hypothesis has yet been offered, and the therapeutic implications of this new etiological approach have not been explored.

The intraocular pressure can be temporarily lowered by rapidly changing the osmotic pressure relations between the ocular fluids and the blood stream (7). Vascular osmotic pressure may be increased by the administration of innocuous crystalloids or colloids in such concentrations as to increase the tonicity of the blood. Readily absorbable substances may be administered orally or rectally, but the intravenous route is preferable, as it avoids the dilution of concentrated solutions in the gastro-intestinal tract. Various hypertonic solutions have been recommended. The use of salt solutions (8) has been generally superseded by less readily diffusible substances, such as glucose (9), sucrose (10), and sorbitol (11). Of these, sorbitol, a complex alcohol, is perhaps the most useful. Bel- lows, Puntenney, and Cowan (11) found that 100 cc. of 50 per cent sorbitol administered intravenously would produce a marked lowering of intraocular pressure for several hours. No harmful effects are known to result from its use (12). The principle use of this method to lower the tension is in the preparation of a glaucomatous eye for operation.

## LOCAL MEDICAL TREATMENT

The mainstay of the medical treatment of glaucoma is the use of drugs locally, usually in the form of eye-drops. These are fortunately well absorbed through



the cornea of the eye, producing a direct effect upon the intraocular structures. The actions in the eye of most of these locally applied medications are related to those of the autonomic nervous system, a fact with deep implications, although we do not fully understand the exact mechanism whereby they lower the intraocular tension.

The fact that certain para-symphathomimetic and symphathomimetic drugs are useful in glaucoma has been known for many decades, but it is only in recent

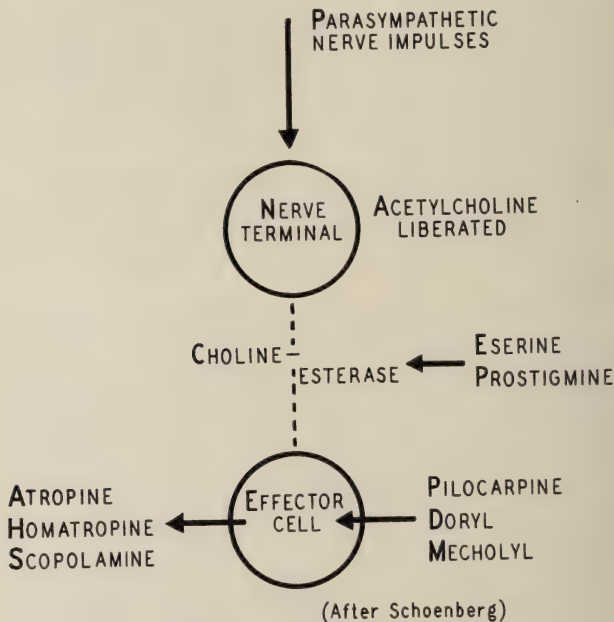


FIG. 1. Schema showing action of parasympathomimetic drugs (See text).

years that any rational approach to an understanding of their mode of action has been gained. This has been largely due to the work of Loewi, Dale and others who have labored so fruitfully in developing evidence of the chemical mediation of nerve impulses (13). It has now been made clear that the parasympathetic nerves act through the liberation of acetylcholine, and that the sympathetic nerves act through the liberation of epinephrine. Normally, acetylcholine is rapidly destroyed by an enzyme in the blood and tissue fluids, known

as cholinesterase. This destructive effect on acetyl-choline of cholinesterase can be prevented by eserine and prostigmine. Parasympathomimetic drugs may therefore act either by direct choline-like action on the motor cell, or by inhibition of cholinesterase. The action of acetyl-choline may be abolished by drugs of the atropine group. Figure 1, adapted from a paper by Schoenberg (14), schematically suggests such modes of action. The para-sympathomimetic drugs are the most useful in treating chronic simple glaucoma. Their classical action is to produce miosis, although other less well understood effects are now believed to play an equal if not more important rôle in the lowering of pathological tension. This latter fact is proven by evidence that intraocular pressure is lowered even in cases where the pupil cannot be constricted (15).

Pilocarpine is still the most popular miotic employed in the treatment of the disease. Its value lies in the fact that while it produces a choline-like effect directly on the effector cells, it is not actually a choline derivative and hence is not inactivated by the cholinesterase of the surrounding media. In the proper dosage it produces a prolonged effect usually lasting about six hours. In addition to lowering the tension of most glaucomatous eyes, although not necessarily to an adequate degree, pilocarpine tends to reduce the lability of the intraocular pressure, as shown by its stabilizing effect on the abnormal tension variations generally encountered in glaucoma (16). The frequency with which pilocarpine should be administered, and its effectiveness, must be determined individually for each patient. An obstacle to its use sometimes encountered is a local sensitivity of the conjunctivae or lids to the drug. A change in the salt of the drug and careful buffering of its hydrogen-ion concentration have been found to overcome this difficulty in most instances.

After pilocarpine, eserine, otherwise known as physostigmine, is the most commonly used drug for chronic simple glaucoma. Its salts were the first drugs used effectively in the treatment of glaucoma, having been introduced by Laqueur in 1876. Its parasympathomimetic effect is attained through the inhibition of cholinesterase, thereby permitting prolonged and intensive action by acetyl-choline. The result of its use in the eye is intense miosis, ciliary spasm and intraocular vasomotor changes, which reach their maximum in about thirty minutes and last for about two hours. The severe contraction of the intraocular musculature may be painful, and may even produce a secondary inflammatory reaction such as iritis, so that the drug must be used cautiously. Its use in chronic simple glaucoma is generally limited to cases where an adjuvant to pilocarpine is indicated.

In recent years, several other miotic drugs have been added to the pharmacological armamentarium. The most important of these are prostigmine, mecholyl, doryl, and furmethide. None of these has been startling in its effects, but all have certain special uses and advantages. Prostigmine acts similarly to eserine, but is more stable, less irritating and more prolonged in its action (17). It may be used where a sensitivity to eserine exists, and has been particularly recommended in conjunction with mecholyl, with which it seems to have a therapeutic synergism (18). Mecholyl, (acetyl-beta-methylcholine chloride) is similar to

acetyl choline in its direct effect on the motor cell, but its action is stronger and of longer duration (19). Clarke (20) suggested its use in chronic simple glaucoma in combination with prostigmine, when some contraindication to the use of more common miotics exists. Doryl (carbaminoylecholine chloride) seems to be the most useful of the newer miotics. It has a choline-like effect that is prolonged and intense, due to its relative invulnerability to cholinesterase (21). It is stable and well tolerated clinically. It controls the tension in some cases where other miotics fail, and its use for short periods seems to enhance the effects of other miotics (22). Doryl does not penetrate the cornea well in ordinary aqueous solution, and its action is enhanced by using a wetting agent, such as zephiran, as a vehicle (23). Furfurmethide (furfuryl-trimethyl ammonium iodide) is the most recently introduced parasympathomimetic. It exerts a direct, choline-like effect on the effector cell and is not affected by cholinesterase (24). The result is a prolonged hypotensive effect on the eye, but it has been found that such action is not dependable over a long period (25).

Those drugs whose action simulates that of the sympathetic or adrenergic nervous system are called sympathomimetics. It has been found that certain members of this group are often locally effective in reducing the abnormal ocular tension of glaucoma. Strong solutions of epinephrine bitartrate and various synthetic substances such as neosynephrine exert a hypotensive effect for varying lengths of time (26). This action is produced differently than in the case of the miotic drugs, and is probably attained initially through vasoconstriction and later by secondary alterations in the circulation in the eye (27). Such action is inconstant and not reliable. There is even a definite risk involved in the use of these substances since an acute congestive glaucoma may be precipitated by the mydriasis they produce, and later rises in tension may be caused by reactive hyperaemia. Such unfortunate complications may usually be avoided, however, by the preliminary use of eserine (28).

#### SURGICAL TREATMENT

The principle involved in most operations for the treatment of chronic simple glaucoma has remained the same for decades. The rationale is to decompress the globe by producing a channel through which some of the intraocular fluid can be drained away. This idea was probably first evolved by deWecker, in 1867. He devised a simple operation termed anterior sclerotomy to produce this effect. The procedures based on this principle are called filtering operations, and practically all are intended to allow aqueous fluid to escape from the interior of the eye to more superficial levels under the conjunctiva, whence it can be more rapidly absorbed by the blood stream. No permanent direct fistulous opening from the eye to the outside is of course feasible, as this would reduce the ocular tension to abnormally low levels, and also be a source of danger through infection.

Three operative procedures are most commonly performed today for the production of this filtration of aqueous, in order to reduce the elevated tension to normal levels. These are performed by either removing a small portion of

sclera near the cornea, making a trephine opening in the eye where the cornea meets the sclera, or by incarcerating a small portion of iris in an opening between the cornea and sclera, enabling aqueous to drain off subconjunctivally.

#### EVALUATION OF RESULTS

Some idea of the results attained in the treatment of chronic simple glaucoma may be obtained from the statistics of the Glaucoma Clinic of The Mount Sinai Hospital. This clinic was organized in 1943 to study and follow the patients under treatment in the hospital and Out Patient Department, and is conducted by Dr. H. Katzin. Records have been kept of seventy-two eyes in forty-four patients. Of these, satisfactory clinical control of the disease has been attained in forty-eight eyes, or 67 per cent of those treated. This was achieved by the local instillation of drugs alone in 26 per cent of all the cases. Of the entire group, forty eyes, or 56 per cent, came to operation after miotics alone had proven inadequate. 63 per cent of the operated cases are now clinically controlled, usually with supplementary use of miotics. Figures such as these are interesting, but must be examined further if any real insight into the situation is to be obtained.

In any study of glaucoma statistics, one fact stands out; namely, that the value of therapy depends largely upon what point in the course of the disease treatment is undertaken. Early cases of glaucoma can generally be arrested, if not by medical treatment, then by operation. Advanced cases,—and “advanced” does not refer to duration but to the degree of pathology present,—respond in a much less satisfactory manner. In a series of cases analyzed by Reese (29) in 1939, forty-six of fifty-one early cases, or over 90 per cent, were arrested by operation. Of one hundred and two late cases, despite operation, sixty-five were failures.

A study of the pathological changes induced by chronic simple glaucoma explains why advanced cases do so poorly under treatment. Clinically, an eye with a visual field under 30 degrees at any meridian, with cupping of the nerve, obliteration of the iris angle, or blood vessel changes, presents evidence of advanced disease. When such an eye is examined histologically, irreversible damage with connective tissue replacement of normal tissues can be demonstrated. Unfortunately, when such a degree of damage has occurred, the process often can no longer be arrested, as a vicious circle of scarring, circulatory embarrassment, and nutritional impairment sometimes has been set up. In these eyes the obliteration of the normal iris angle and drainage tracts produces abnormal tension, and the increased intraocular pressure produces more damage in many cases, no matter what procedures are undertaken. Cavernous degeneration of the optic nerve occurs, and proliferation of interstitial connective tissue produces scar tissue that occupies the cupped disc. An obliterating endarteritis often is found in retinal arterioles, and the degeneration so initiated goes on to destroy vision despite subsequent procedures that may lower the tension.

Since the results of early treatment of chronic simple glaucoma are usually

satisfactory, the most pressing problem in the public health aspect of the disease is why certain cases are permitted to go on untreated, to such hopelessly late stages. The three principal reasons are: (1) deliberate neglect of the disease, (2) failure of early diagnosis, (3) postponement of operation where necessary. All of these are attributable to ignorance.

#### CAMPAIGN OF EDUCATION

The early diagnosis of disease, and provision for the adequate medical attention which it requires, are matters which concern the general public quite as much as the medical profession. The situation is not strictly analogous to cancer, where the earlier the operation the better the result, but in some instances it may be very similar. Certainly one of the most important advances in the therapy for glaucoma has been the campaign of education by the National Society for the Prevention of Blindness, to acquaint the laity, and the general practitioner, with the need for early diagnosis and proper observation.

#### EARLY DIAGNOSIS

There have been gratifying advances in recent years in the earlier and more accurate diagnosis of this disease. More refined methods of plotting visual fields with the minute test objects of Evans, now give us information that takes some patients with borderline tensions out of the doubtful group. Patients are now hospitalized and ocular tension curves studied at frequent intervals over the entire day and night, to detect an abnormal rise that might be missed in a single office or clinic visit. A diagnostic test recently reported from this institution by Bloomfield and Lambert (30) demonstrates an increased lability of the ocular tension in very early or incipient glaucoma. This method for estimating the efficiency of ocular tension regulation in any eye may have some value not only in diagnosis but in evaluating the efficiency of therapy.

#### PSYCHOSOMATIC POSSIBILITIES

There is much evidence that chronic simple glaucoma may be one of that group of illnesses that includes Graves' Disease, peptic ulcer and hypertension; where psychic disturbances play an important rôle in pathogenesis (31). For years, most ophthalmologists have recognized that the acute congestive type of glaucoma may be precipitated by mental shock or emotional disturbances. This factor has not been so obvious in chronic simple glaucoma, although some observers have noted what appear to be definite psychosomatic relationships. The papers of Inman (32), Schoenberg (33) and others called the attention of the profession to this phase of the problem. While conclusive evidence has not been forthcoming, their reports have been most stimulating to thought.

In this institution, trained investigators are now studying this important phase of the problem of chronic simple glaucoma. This work was begun one year ago and the Rorschach Test was selected as a useful means for determining the character structures of patients with this disease. The tests are administered and analyzed by Mrs. M. Levi under the supervision of Dr. E. G. Schachte<sup>1</sup>



The material is then presented to Dr. S. W. Ginsburg, Associate Psychiatrist to the hospital, for review and criticism.

As the work progresses, it is hoped to include a large proportion of the available cases and to complete a series of control tests which have just been started. Two control groups are to be studied; namely, patients with eye diseases other than glaucoma, and patients of the equivalent age group chosen at random from the General Medical Clinic. As time goes on, it is also planned to investigate a certain number of these patients psychoanalytically in conjunction with their Rorschach Tests.

Although it is much too soon to make any definite statements, Mrs. Levi has made certain preliminary observations which seem to be suggestive. In general, all the patients studied have had more or less overt anxiety, and were consistent in having feelings of insecurity and helplessness to some degree. Strikingly, about a third of the patients studied had a deep-seated anxiety neurosis, which seemed of long standing and undoubtedly antedated the glaucoma. It is to be hoped that from such an investigation the psychosomatic background for chronic simple glaucoma may be clarified and a psychotherapeutic approach to treatment of appropriate cases elucidated.

While much has been accomplished in the development of the treatment of chronic simple glaucoma, the greatest obstacle to a completely satisfactory therapeutic approach has been the lack of understanding of its basic nature. Further advances will follow as systematic studies of its cause and pathogenesis bear fruit. Certain leads are unfolding, such as the mechanism of the hypotensive effects of choline derivatives and their sites of action. On the other hand, the concept of an autonomic center for intraocular pressure suggests that a breakdown (on a presenile or degenerative basis) may preclude a basic cure for the disease. Finally, specialized problems, such as that of the aqueous veins, goniotomy, intraocular fluid dynamics, and many others, present themselves.

Perhaps the most effective single measure for the control of the disease in the immediate future is the education of the public to the need for early diagnosis and treatment, and proper care and observation. It is in this field that the efforts of the National Society for Prevention of Blindness have been so commendably effective.

#### REFERENCES

1. SMITH, V. M.: Staff. Assoc. Nat. Soc. for Prevention of Blindness. The Merck Report. October, 1944.
2. Rules for Glaucoma Patients. Committee on Glaucoma. Nat. Soc. for Prevention of Blindness, New York.
3. JOSEPHSON, E. M.: Eye, Ear, Nose & Throat Monthly, 13: 453, 1935.
4. MILLER, E. A.: Am. J. Ophth., 22: 536, 1939.
5. ALVIS, E. B.: Am. J. Ophth., 23: 529, 1940.
6. ELWYN, H.: Arch. Ophth., 19: 986, 1938.
7. LAMBERT, R. K., AND SILBERT, S.: J. A. M. A., 90: 1435, 1928.
8. LAMBERT, R. K., AND WOLFF, J.: Arch. Ophth., 2: 148, 1929.
9. GIFFORD, S. R.: Handbook of Ocular Therapeutics, ed. 3, Philadelphia, Lea & Febiger, 1942, p. 310.

10. DYAR, E. W., AND MATTHEW, W. B.: Arch. Ophth., 18: 57, 1937.
11. BELLWS, J., PUNTENNEY, I., AND COWAN, J.: Arch. Ophth., 20: 1036, 1938.
12. LINDBERG, H. A.: Cited by Gifford, S. R. (9) p. 311.
13. GUYTON, J. S.: Arch. Ophth., 24: 555, 1940.
14. SCHOENBERG, M. J.: Am. J. Ophth., 26: 1282, 1943.
15. FEIGENBAUM, A.: Arch. Ophth., 5: 261, 1931.
16. THIEL, R.: Cited in Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Co., 1941, vol. 3, p. 3394.
17. DUKE-ELDER, W. S.: Textbook of Ophthalmology, St. Louis, C. B. Mosby Co., 1941, vol. 3, p. 3395.
18. CLARKE, S. T.: Am. J. Ophth., 22: 294, 1939.
19. Ibid.
20. Ibid.
21. CLARKE, S. T.: Am. J. Ophth., 25: 309, 1942.
22. Ibid.
23. O'BRIEN, C. S., AND SWAN, K. C.: Arch. Ophth., 27: 253, 1942.
24. MYERSON, A., AND THAU, W.: Arch. Ophth., 24: 758, 1940.
25. UHLER, E. M.: Am. J. Ophth., 26: 710, 1943.
26. RISER, R. O.: Arch. Ophth., 32: 70, 1944.
27. DUKE-ELDER, W. S.: (18) 3: p. 3396.
28. GIFFORD, S. R.: (10) p. 305.
29. REESE, A. B.: J. A. M. A., 113: 1204, 1939.
30. BLOOMFIELD, S., AND LAMBERT, R. K.: In print.
31. DUNBAR, H. F.: Emotions and Bodily Changes. New York, Columbia University Press, 1938, p. 365.
32. INMAN, W. S.: Lancet, 2: 1188, 1929.
33. SCHOENBERG, M. J.: Arch. Ophth., 23: 76, 1940.

## A DISTINCTIVE BUT FREQUENTLY UNRECOGNIZED VARIETY OF RINGWORM OF THE SKIN

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It is only within the past few years that fungus infections, in contrast to bacterial diseases, have attracted much notice. Very little attention has been focused on the extremely wide range of diseases which are due to mycologic agents. The popularization of the term "athlete's foot", the return of war casualties with tropical fungus diseases and the discovery of the amazing properties of the fungus product, penicillin, are among the most recent developments leading to a renewed interest in mycology. The diagnosis of fungus infections usually requires complex laboratory techniques and may only be performed with extreme difficulty. However, different fungus diseases have certain definite features which may suggest the etiologic agent from a clinical standpoint and thereby simplify the selection of the proper laboratory procedure. For example, ringworm of the scalp due to "animal" fungi usually appears as scaling patches of brittle hairs. Pustules are found around hair follicles, the hair is easily removed and the patches are inflammatory. With infection due to the "human" type of fungus, pustules are rarely observed, hairs are not easily extracted and the patches are not inflammatory. These clinical differences are then corroborated by microscopic examination of the hair, observation under filtered ultraviolet radiation, trichophytin tests and cultural studies. With the aid of similar procedures, it has become possible to recognize that certain infections of the skin may be due to a specific vegetable parasite from the clinical features alone. In the past, it has been customary to group a wide variety of fungus infections of the non-hairy skin under the heading of *tinea circinata* or ringworm of the body. This group was divided into two parts, namely the dry and the moist. The dry form of the disease was usually described as one or several, pea to large-coin-sized reddish circles with a pale center. It was this unaffected pale center with the raised periphery that was responsible for the term "ringworm". The moist form of the disease was represented by vesicular and pustular lesions. In the usual instance, pinpoint sized vesicles sprang from a central point and rapidly spread outward to form an enlarging circle. These evolved in similar fashion to the dry forms but usually maintained their active vesicular borders. As a rule, the eruption was trifling but may have been quite extensive due to the confluence and extension of several lesions. In addition to these main types, numerous variants were included with the original descriptions. From this scrap-basket designation, various entities have been gradually removed and some of these included such diseases as favus, moniliasis, blastomycosis, erythrasma, *tinea versicolor*, *tinea imbricata*, *chromoblastomycosis* and others too numerous to mention. The purpose of this article is to describe the manifestations of one of the lesser known members of the family of fungi which produce ringworm of the body, namely *trichophyton purpureum*.

This organism produces a clinical picture which is so characteristic that an etiologic diagnosis can usually be made from the superficial appearance alone. This is of importance both as to prognosis and therapy.

#### CHARACTERISTICS OF THE FUNGUS (*T. PURPUREUM*)

*Historical*—The fungus was first described in 1910 by Castellani (1). He called it epidermophyton rubrum because the cultures on glucose agar were red. They also showed a central knob or a crateriform appearance. Almost simultaneously, Bang (2) cultivated a species which he called trichophyton purpureum. On glucose agar, these colonies were white with an elevated center. The characteristic red color could only be seen on transillumination of the deep layer of the colony or from the back of the culture. Notwithstanding the different features described by these mycologists, Saboraud (3) expressed the opinion that the organisms were identical. The excellent work of Lewis (4) on the laboratory and clinical phases of the disease has lent proof to this observation.

*Laboratory Observations*—Microscopic examination of scrapings from cutaneous lesions may show a few mycelial fragments. These are neither characteristic nor diagnostic. Cultural studies must be performed, and it may be necessary to culture repeatedly the lesions before the organism can be isolated. If the nails are involved, it is important to obtain material from their deeper strata inasmuch as the fungus is hardly ever found superficially in nail tissue. In typical cases the cultural growth begins in several days as a fluffy white speck on dextrose agar. In one to two weeks, the colony appears as a downy or fluffy white culture with a lilac or deep red color best seen from the back. Under the filtered ultraviolet radiation, a rather typical blue border is usually observed. The microscopic culture mounts are not specific and show tortuous mycelia with occasional small conidia. The trichophytin test may be weakly positive or even negative probably due to the lack of development of immune bodies to this infectious agent. The histopathologic findings are similar to those of other cutaneous fungus infections and consist merely of a superficial inflammatory process of little diagnostic import.

*Clinical characteristics of the infection.* This fungus is responsible for a clinical picture whose features enable one familiar with it to suggest an immediate diagnosis. The eruption may consist of few or many lesions. These lesions are usually nonelevated, erythematous-squamous patches of various size and shape with an extremely well defined border. The erythema is of a dull, lustreless sheen and is uniform throughout the patch. The covering scale is thin and superficial. The border is sharply defined and unlike most superficial fungus infections of the body, it shows no signs of a vesicular border. The affected areas and especially the border are usually infiltrated. This elevated border may be so evident as to resemble the lesions of erythema annulare centrifigum or even an annular lichen planus. The favorite locations are the hands, feet and groin. Unlike most fungus infections of the feet, the involvement may be along the medial or lateral aspects although the interdigital spaces are frequently involved. The lesions involving the groin resemble those of tinea cruris except for the ab-

sence of a vesicular margin and the lack of central clearing. The toe nails, and the finger nails to a lesser degree, are commonly involved and like other forms of onychomycosis are discolored, filled with crumbly material and dystrophic. Repeated observations lead us to concur with Lewis in that neither concomitant involvement of the toe webs nor paronychia are encountered in association with ungual infections due to *T. purpureum*. This organism rarely gives rise to infection of the hair follicles although we have isolated it in pure culture from two cases of ringworm of the bearded region.

#### CASE REPORT

*History:* G. L., a woman, aged 41 years, was first seen on September 3, 1943. There was nothing of importance in the past, personal or family history except for "nail trouble" over a period of years. The present illness began several months before the initial observa-



FIG. 1. Scaling lesion on dorsum of hand. The sharply defined, elevated margin is characteristic.

tion and appeared as red, scaling patches on the hands, feet and anterior aspects of the legs (figs. 1 and 2). These patches gradually increased in size and spread to the forearms, arms and thighs. The patient applied various local preparations without influencing the eruption in any manner.

*Examination:* The skin showed numerous erythematous-squamous patches on the upper and lower extremities. These lesions were dull red in color and 1 to 8 cm. in diameter.





FIG. 2. Scaling lesion with well defined margins on leg.



FIG. 3. Scrapings from patient infected with *T. purpureum*. The examination shows branched mycelia and arthrospores.

The surface was covered with a fine branny scale and the border was sharply defined. There was no evidence of vesiculation or of central clearing. Several nails of both hands and feet were opaque, yellowish-brown and friable. The nail plates were separated and filled with a thick, yellowish, hyperkeratotic material.

*Laboratory data:* Microscopic examination of scrapings in lactophenol with cotton blue revealed numerous mycelia which were long, wavy and septate (fig 3). Scales were planted in dextrose agar and gave typical fluffy white cultures with lilac undersurfaces and knob-like, elevated centers (fig. 4). The purple-reddish color was particularly evident on transillumination. Culture mounts revealed tortuous mycelia with interspersed small conidia

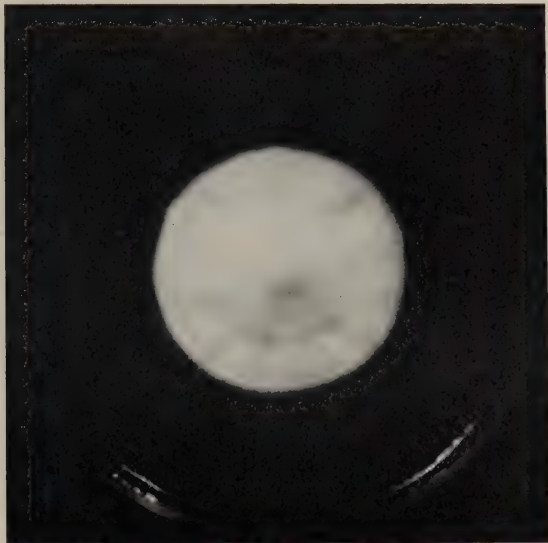


FIG. 4. Culture of *T. purpureum*, age one month. Note knob at center.

(fig. 5). Under the Wood's filter the culture showed a bright blue fluorescence. The colony eventually exhibited pleomorphism.

*Treatment:* The lesions were treated locally with several fungicidal and keratolytic agents. They showed progressive improvement following repeated applications of a solution containing five per cent salicylic acid and two per cent thymol, and an ointment containing soft soap, resorcinol and sulfur. The nails improved slowly with mechanical abrasion, copper sulfate iontophoresis and salicylic acid plasters.

*Therapy.* Fungus infections due to *T. purpureum* are among the most obstinate and rebellious skin lesions to cure. Treatment must be continued over prolonged periods of time and modified according to the changes observed in the skin. The organisms which ordinarily produce ringworm of the glabrous

skin respond readily to ointments containing five to ten per cent sulfur, ammoniate of mercury and combinations of benzoic and salicylic acid. Unfortunately, this does not apply to infections of this type. In our experience, the most effective parasiticides in this disease include combinations of pyrogallol, betanaphthol, thymol, iodine, salicylic acid, resorcinol and chrysarobin. The roentgen rays are of value only in the presence of secondary eczematization and lichenification. The diseased nails offer a peculiar focal problem due to their relationship to recurrences and exacerbations. Surgical evulsion is usually followed by prompt recurrence of the disease in the newly formed nail. We are more apt to apply gradual mechanical debridement (dental burr, glass slide) following



FIG. 5. Culture mount of *T. purpureum*. Many microconidia, both grappes and thyrsi, are evident.

applications of potassium hydroxide or salicylic acid plasters. Fungicidal agents which are also keratolytic in effect, may also be applied. Iontophoresis with copper or zinc sulphate in conjunction with the remedies listed above may also lead to improvement. The patient must be informed as to the chronicity of this particular infection and the importance of continuing local applications for prolonged periods of time. Immunologic methods of therapy are of no value. It has often been said that the treatment of skin disorders is unsatisfactory because the preparations used are too strong. In this disease, however, it is important to make the proper diagnosis so that stronger remedies will be employed early. If this does not occur, the patient will usually become discouraged due to the application of weak and ineffectual drugs when Herculean remedies are essential from the time of the initial observation. We believe that some of our

patients did not respond properly to therapy because of the employment elsewhere of weak concentrations of various drugs to which they acquired a tolerance and subsequent therapeutic impotency.

#### SUMMARY

A report is made of a typical case of ringworm of the body due to *T. purpureum*. The fundamental characteristics of the disease produced by this organism are enumerated. Some of the features of this disease are so characteristic as to enable the trained observer to make an etiologic diagnosis from the clinical findings. A brief description of the gross and microscopic pathological changes produced by this fungus is included. It is to be emphasized that this disease shows unusual resistance to treatment. For this reason, it is of the utmost importance that early diagnosis and adequate therapy be employed.

#### BIBLIOGRAPHY

1. CASTELLANI, A.: *Brit. J. Dermat.*, 22: 147, 1910.
2. BANG, H.: *Ann. de dermat. et syph.* 1: 225, 1910.
3. SABOURAUD, R.: *Brit. J. Dermat.* 23: 389, 1911.
4. LEWIS, G. M., MONTGOMERY, R. M., AND HOPPER, M. E.: *Arch. Dermat. & Syph.* 37: 823, 1938.

## RECENT ADVANCES IN CANCER RESEARCH<sup>1</sup>

RICHARD LEWISOHN, M.D.

It is impossible in the short time of a lecture to review even the most recent advances in Cancer Research.

Cancer Research is carried on all over the world in institutions especially built or equipped for this purpose or in smaller units affiliated with general hospitals. Their number cannot be given accurately.

The literature which has been accumulated on this subject is so vast that it is impossible for any one person to be familiar with all its different phases. A recent bibliography, published by the International Cancer Research Foundation, lists over 12,000 individual papers and monographs which appeared between 1900 and 1935—certainly a definite proof of the enormous amount of effort and endeavor which has been put into cancer research.

In this lecture, I shall confine myself to a discussion of three different groups of cancer research: 1) A review of some recent work on carcinogenic substances, 2) a discussion of the relationship of sex hormones to carcinogenesis, and 3) a brief report of the work of the Cancer Research Laboratory of Mount Sinai Hospital in cancer therapy.

### 1. CARCINOGENIC SUBSTANCES

In recent years great progress has been made in the production of cancerous growth in laboratory animals by known chemical agents, i.e., carcinogenic substances. Let us review briefly one group of such substances, namely, the aromatic hydrocarbons.

The aromatic hydrocarbons are composed of several benzene nuclei (Fig. 1a); the benzene nucleus is commonly presented by a hexagon, numbering the substituent groups in order of their respective carbon atoms (1b). Three such hexagons fused together form the anthracene nucleus (1c). Substituting in the position 1-2 and 5-6 one hydrogen by one benzene nucleus, we have a pentacyclic compound, called 1,2,5,6 Dibenzanthracene (fig. 1d), a highly potent carcinogen. Four hexagons arranged as presented in figure 1e, are called pyrene; if one more hexagon is added in the 3,4 position, we arrive at 3,4 benzpyrene (fig. 1f) which is one of the most potent carcinogenic compounds. This particular compound has the distinction of being the only carcinogenic hydrocarbon which so far has been isolated directly from the coal tar (18).

Substituting into the anthracene nucleus in position 1-2 (1g) one benzene nucleus, we arrive at 1:2 benzanthracene (1h) which leads to a compound called cholanthrene (1i). Replacing one hydrogen of this compound in position 20 by a methyl group ( $\text{CH}_3$ ) we arrive at 20-methyl cholanthrene (1k) which is a highly potent carcinogen.

<sup>1</sup> From the Cancer Research Laboratory, Department of Pathology, The Mount Sinai Hospital. Lecture delivered at the Blumenthal Auditorium, January 24, 1945.



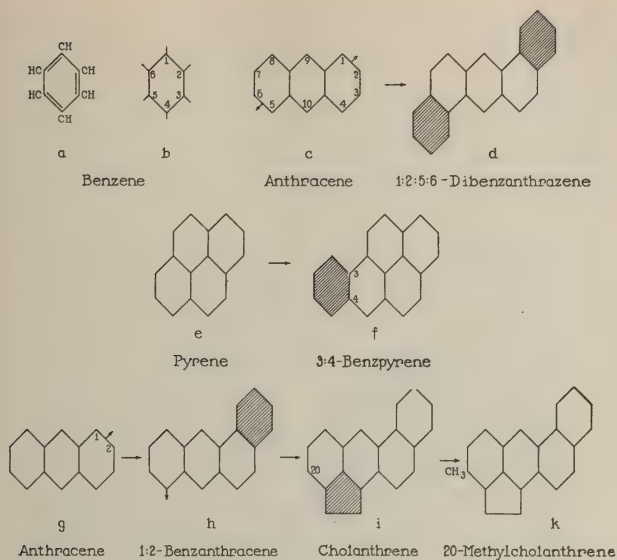


FIG. 1. Carcinogens

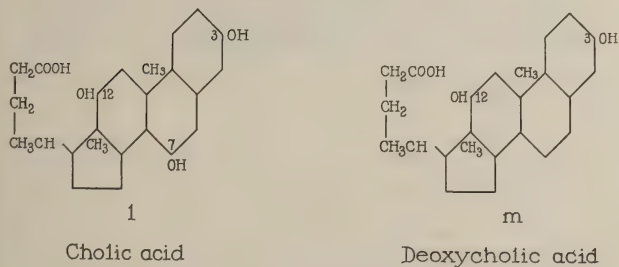


FIG. 2. Bile acids

Let us now review briefly the chemistry of the bile acids, namely, cholic acid and deoxycholic acid (fig. 2m).

We observe a close structural similarity between these two compounds and the

above mentioned methylcholanthrene. Indeed Fieser and Newman (19) succeeded in converting cholic acid into methylcholanthrene by chemical methods. The conversion of the physiologic bile acids into a highly potent carcinogen is most significant.

Why did the chemists become interested in these aromatic hydrocarbons? Percival Pott (20) described, in 1775, the chimney sweep's disease and attributed it correctly to the irritation of the scrotal skin by coal soot, deposited in the chimneys. In 1915, two Japanese scientists, Yamagiva and Itchikava, (21) proved that coal tar, rubbed into the skin of animals will produce cancers. From 1924 on, Kennaway and his associates (22) started to prepare various fractionation products of coal tar and tested these for their carcinogenic activity. A large number of synthetic carcinogenic compounds was prepared and one substance, namely, 3,4 benzpyrene, was isolated from coal tar. Through the efforts of this group, the Harvard group under Fieser (23) and the National Cancer Institute (Andervont (24), Shear (25) and Shimkin (26)), many carcinogenic substances were discovered. The relationship between chemical structure and carcinogenicity was studied. The potency of various active compounds was estimated and the influence of hereditary factors upon the formation of tumors by these hydrocarbons was examined. The mechanism of detoxification and elimination of the carcinogenic substances in various animal species was investigated (Boyland (27), Dobriner and Rhoads (28)).

These series of investigations clarified a number of problems, which I would like to mention briefly: The time period elapsing between the application of the carcinogen and the first occurrence of tumors depends on the potency and quantity of the carcinogen, on the solvent in which the carcinogen is applied, on the mode of administration to the experimental animal and also upon the strain of animals used. However, when once optimal conditions are reached, the latent period cannot be shortened and will last several weeks.

Furthermore, the latent period, frequency of tumor occurrence and the type of tumor tissue formed, depend on the mode of administration (subcutaneous or intravenous administration, etc.) even when applying one carcinogen in one uniform dose to one animal strain.

Although a large number of carcinogenic substances of various potencies are known, no definite relationship between structure and carcinogenicity exists. Structurally closely related hydrocarbons differ considerably in their potency.

In a recent publication Cramer and Simpson (29) described a considerable increase in mast cells in the epidermis after painting the skin with methylcholanthrene. This increase in the mast cells was observed long before skin cancers appeared and as a matter of fact was especially strong in the epidermis of mice which later did not develop cancers. The authors feel, that the mast cell reaction is associated with a defensive process against the development of skin cancer. Early chemical changes in the epidermis, after methyl cholanthrene painting, were described by Carruthers and Sontzeff (30): 10 days after the painting the calcium content of the epidermis dropped considerably.

Tumor formation does not regularly depend on the local irritation. Strong

local irritants are not necessarily carcinogens. For instance, mustard gas, a strong skin irritant, has no carcinogenic properties. On the contrary, it inhibits the carcinogenicity of coal tar (Berenblum (31)).

Heredity and sexual maturity of the animals have a strong influence upon the latent period and the yield of the tumors. We pointed out previously the chemical relationship between 20-methylcholanthrene and the bile acids. A number of other normal constituents of the animal and human body such as cholesterol, vitamin D, male and female sex hormones are also structurally related to methylcholanthrene. There is however, no experimental evidence available at present

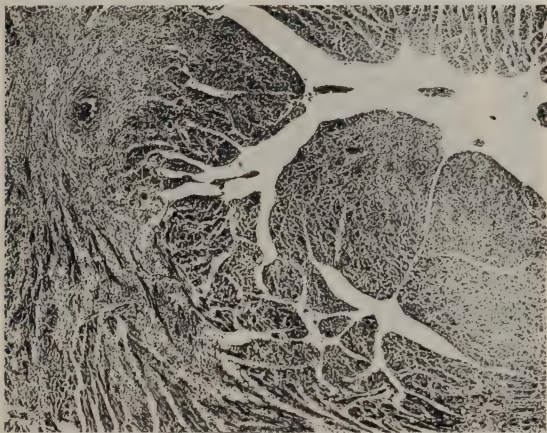


FIG. 3. Low power view of a heart 5 months after one subcutaneous injection of colloidal benzpyrene. This section shows severe diffuse myocarditis. A large branch of the coronary artery participates in the process. (Arch. Pathology, 1941.)

which would prove or even suggest the conversion of a naturally occurring compound into a carcinogen in the body. The possibility of such conversion under abnormal metabolic conditions was repeatedly stressed and has to be considered in future research.

Paradoxically carcinogenic substances retard the growth of certain transplanted and spontaneous neoplasms (Haddow (32)). They retard apparently the body growth of young animals. In certain concentrations they inhibit a variety of enzymatic reactions. In this laboratory, generalized vascular and visceral lesions in mice following a single subcutaneous injection of benzpyrene were observed by R. Leuchtenberger. These lesions occurred about 2-4 months after the injection and were of an inflammatory nature. They occurred in 64 per cent of the mice in which no tumors developed after the injection of benzpyrene, as

compared with only 25 per cent in the tumor mice. The lesions encountered were either a nodular periarteritis, a necrotising panarteritis, or a diffuse myocarditis. Occasionally, they consisted of an extensive tumor-like proliferation of the reticulo-endothelial tissue within liver and spleen with infiltration into the wall of large vessels and destruction of the parenchyma (figs. 3 and 4).

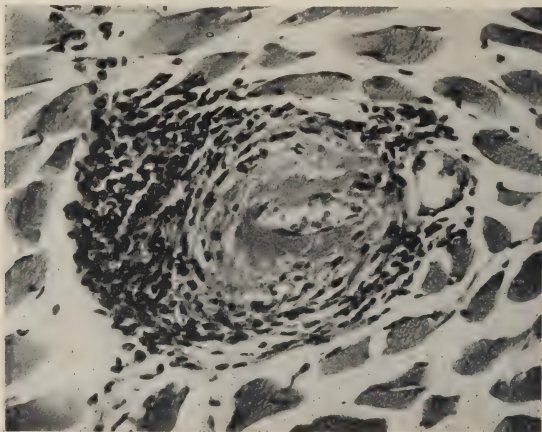


FIG. 4. Microscopic section of an artery in the diaphragm, 4 months after one subcutaneous injection of colloidal benzpyrene, showing necrotizing arteritis. Similar lesions are seen in the blood vessels in other parts of the body.

## 2. RELATION OF SEX HORMONES TO CARCINOGENESIS

For a long time the sex glands have been suspected of being closely connected with cancerous growth. A large number of experiments in animals, dealing with this problem, seemed to support this conception, especially the studies of Lathrop and Loeb (33), Cori (34) and Murray (35), who observed that ovariectomy in mice at an early age prevents the appearance of mammary tumors and proved definitely the decisive influence of the ovaries on mammary cancer in mice. Since the isolation and chemical characterization of the sex hormones, research in this field was of course greatly stimulated. As it is impossible to discuss in detail the numerous studies and attempts which have been made to clarify the relation between sex hormones and carcinogenesis, I am going to present here only the main trends and advances in this field.

### *I. Influence of female sex hormones on cancer formation*

In 1932, Lacassagne (36, 37) first reported a carcinogenic effect of estrogen on the mammary gland. In his strain, breeding female mice showed a high inci-

dence of mammary tumors, while male mice of this strain never developed tumors. If these male mice were treated with folliculin, shortly after their birth, and the injections continued at weekly intervals, mammary tumors were observed in these male mice. The experiments of Lacassagne have been confirmed by many investigators, who also showed that male mice, from strains in which the females develop tumors, acquire such tumors after the injection of estrogens.

In some strains the mammary cancers occur earlier following treatment with estrogen than in the untreated animals. Furthermore, the incidence of cancer is usually increased, or the tumors appear earlier in the estrogen treated animals than in the controls. If estrogen is administered to mice from a strain in which no tumors appear spontaneously, tumors are observed very rarely. The stimulation of neoplastic processes by estrogens was also described in rats by Geschickter and Byrne (38). They reported that among 555 rats treated with estrogens, 202 developed mammary cancers. Untreated rats of the same colony did not develop mammary tumors. The larger the dose of the hormones, the earlier the tumors appeared. Tumors in other locations were also observed after prolonged estrogen treatment. Gardner and associates (39) reported the appearance of spindle cell sarcomas at the sites of injections of estrogens. Pybus and Miller (40) observed an increased incidence of bone tumors in male mice from a strain in which the females showed a high incidence of bone tumors and earlier appearance of bone tumors in the females. Lacassagne (41) and Gardner (42) reported the appearance of lymphoid tumors after estrogen treatment. Gardner also described the frequent appearance of hypophyseal tumors in the strain of mice, while in other strains the appearance of hypophyseal tumors had not been observed. Although large doses of estrogens have been administered to animals of other species, (rabbits, dogs, monkeys), no malignant growth has been observed.

The effect of estrogens on the growth of various transplanted animal tumors has also been studied. Although there are some contradictory results which even report inhibition after estrogen injections, the majority of the experiments show the stimulating effect of estrogens on the growth of tumors. It was also shown that estrogen treatment increased the susceptibility to carcinogenic substances, resulting in earlier appearance of tumors in the estrogen treated animals than in the controls. In male rabbits estrogen treatment also stimulated the growth of Brown-Pearce carcinoma and enhanced its metastasis formation.

Estrogens of different chemical structures have been used in all these experiments and similar results have been obtained. For instance, a synthetic estrogen, stilbestrol, which does not occur naturally and is not even chemically related to the sterols of the naturally occurring estrogens, has been found capable of inducing mammary tumors in the same way as the naturally occurring estrogens. This observation indicates that there is apparently no chemical specificity of the estrogens for the carcinogenesis, but the biological effect produced by these substances seems to determine their carcinogenic activity. Up to the present, the mechanism of the estrogenic activity is not too well understood and varied opinions have been expressed. The assumption which appears to come closest to the experimental findings is that estrogens induce hyperactivity of certain specific tis-



sues, sensitizing them to the action of carcinogenic factors, either inherent or exogenous.

The display of carcinogenic activity of the estrogenic hormones in animals deserves some special attention in view of the widespread clinical use of estrogenic substances in humans. Though Zondek and other investigators never observed tumor development in female patients after long treatment with estrogen, it seems justified to use great care when estrogenic substances are given in high doses for a long period of time.

## *II. Influence of the male sex hormones on tumor growth*

Nathanson and Andervont (43), Lacassagne (44) and others showed that injections of testosterone at an early age into female mice of a strain with a high tumor incidence, reduced the incidence or impeded the appearance of the tumors. This tumor inhibiting influence of the male sex hormone seems to be limited to cases in which it might possibly effect spontaneous tumor formation by inhibition of the estrogenic activity. The observations of Gardner that testosterone in very large amounts decreases the incidence of mammary tumors in estrogen treated animals also speak for the counteracting influence of testosterone on the estrogenic activity. In transplanted or chemically induced tumors testosterone did not show an inhibitory influence on the tumor growth.

In the human, the male sex hormone seems to promote the growth of the prostatic cancer. Time does not allow us to discuss this most interesting subject which has recently created wide discussion.

## 3. STUDIES IN THE THERAPY OF CANCER

In the work which I shall present to you, I was fortunate to have associated with me Mrs. C. Leuchtenberger (as biologist), Dr. R. Leuchtenberger (as pathologist), and Dr. D. Laszlo (as biochemist). Our group has worked intensively on this problem for more than seven years. Any progress in this difficult field of cancer therapy which we may have achieved is the result of the endeavors of this group. Dr. K. Bloch and Dr. Z. Dische joined our group for one and two years respectively. During the last seven years we have published a number of papers. In presenting this review of our work, I shall quote occasionally from previous publications.

In the course of this report, I shall have to refer repeatedly to experiments performed on transplanted and spontaneous malignant tumors in mice. Thus it appears appropriate to discuss here the advantages and disadvantages of these two groups of tumors.

*Transplanted tumors:* In a transplanted tumor, a very small piece of fresh tumor tissue is inserted subcutaneously by means of a trocar into normal mice or rats. This tiny piece of tumor tissue grows rapidly in the host. Within 8 to 10 days it has changed into a tumor of 1-2 cm. which lends itself readily to therapeutic experiments. The great advantage in working with transplanted tumors is the fact that these tumors are available at any time in large quantities. However, it must be born in mind that these tumors are produced artificially. They

are transplanted into the host, not produced by the host. In the early years of cancer research most of the research work on malignant tumors was done on transplanted tumors. During the last 20 years, the transplanted tumor has become discredited for some very good reasons. It is, as just stated, not a cancer produced by the host. Furthermore, many of these transplanted tumors, while growing fast and steadily at the start, show definite signs of spontaneous regressions and complete disappearance in untreated controls. Thus, the evaluation of any new therapy becomes very difficult and subject to errors. However, transplanted tumors are of greatest importance for cancer research, as the supply of spontaneous cancers in mice is limited. Many problems could not have been

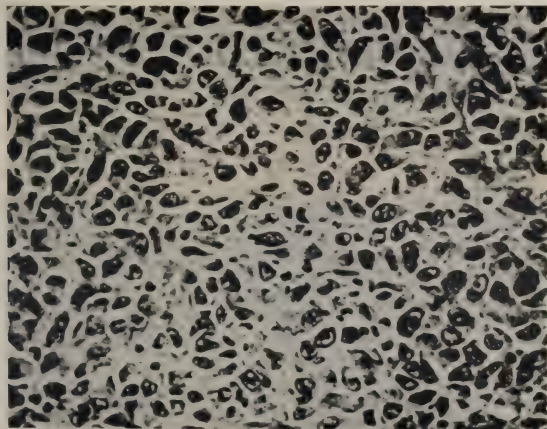


FIG. 5. Microscopic section of untreated sarcoma 180 (Surgery, Gynecology, and Obstetrics, 1938.)

attacked without the use of transplanted tumors. For instance, the bioassay test which Laszlo and Leuchtenberger worked out in this laboratory and which has helped us greatly in the progress of our therapeutic studies depends on the growth-rate of transplanted tumors (see below). In our work with transplanted tumors, we have used the so-called Sarcoma 180 which is really a carcinoma, derived originally from a breast carcinoma of a mouse (fig. 5).

*Spontaneous Tumors:* In the mouse, breast tissue is found not only on the front of the chest and abdomen, but on the dorsal side of the body (fig. 6). Therefore breast cancers can be found not only in front or on the sides of the animals, but also on the back. Spontaneous malignant tumors in mice occur practically exclusively in the breast. The vast majority are adenocarcinomas (fig. 7). They metastasize frequently (about 15 per cent) into the lungs. Metastases in other

organs are very rare. We have observed a large number of spontaneous breast cancers in mice. During a period of about six years, we have treated more than 6000 spontaneous tumors. We have learned that palpation alone is not sufficient

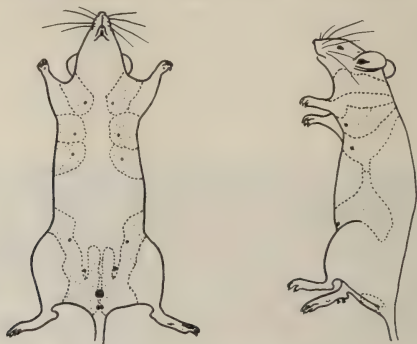


FIG. 6. Location of breasts in a mouse

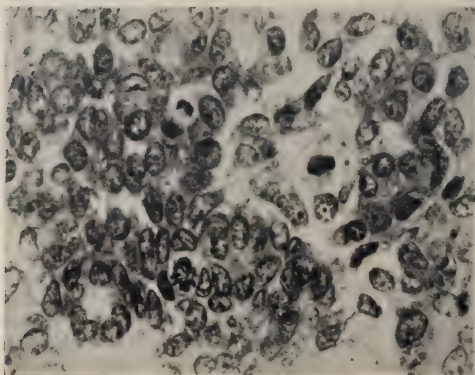


FIG. 7. Spontaneous tumor. Mouse adenocarcinoma (strain A). High power showing several mitoses (Surgery, Gynecology, and Obstetrics, 1940).

to establish the diagnosis of malignancy. Palpatory findings are subject to error even in the hands of experts, exactly like in human pathology. Thirteen per cent of these tumors are not carcinomas (milk cysts, abscesses, benign tumors, etc.). For this reason, we have biopsied every tumor before treatment. A tiny piece of



FIG. 8. Control. Jackson Memorial Laboratory, (1) (Left) July 19, 1939: Biopsy: Carcinoma. (2) (Center) and (3) (Right) Front and lateral view of same tumor after 2 months (September 27, 1939).



FIG. 9. Control. Jackson Memorial Laboratory, (1) (Left) August 3, 1939: Biopsy: Carcinoma, (2) (Right) Size of tumor on September 27, 1939.

tumor is removed under general anesthesia. Any negative or doubtful case is excluded.

Some of our critics have suggested that our therapeutic results were due to the biopsy and not to the chemicals used. Experience in human pathology does not substantiate this claim. It is well known that in patients a biopsy tends to spread the growth of cancer cells. For this reason biopsies of breast cancers in patients, when proven to be malignant, are followed immediately by radical mastectomy.

However, in order to disprove this point definitely, we subjected 374 mice with breast cancers to biopsy. No intravenous treatment was given. In four of these

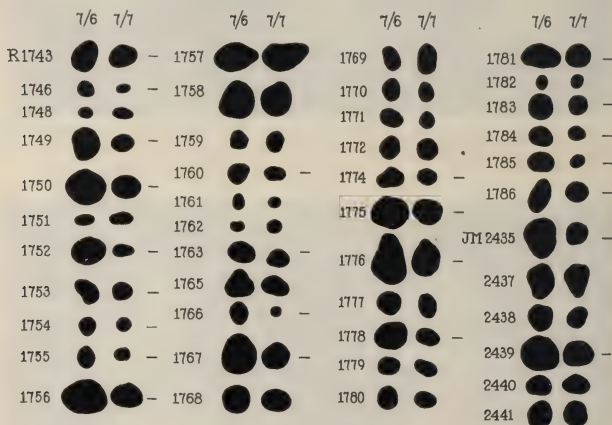


FIG. 10. Effect of biopsy and treatment on spontaneous breast cancers.

374 animals, the tumors regressed completely following the biopsy (1%). The remaining 370 animals died, the majority of them with multiple or with very large tumors (figs. 8, 9 and 29).

It has been our custom to start treatment on the day of the biopsy. Early reduction in the size of the tumor is, in the majority of cases, due to treatment and not, as has been stated, due to the biopsy. Figures 10 and 11 illustrate this point very well. Among 45 tumors biopsied and treated the same day, 24 showed marked reduction in size when measured the next day, whereas among 30 biopsied controls only 4 tumors showed diminution in size.

We used to work for a number of years exclusively with strain A mice from the Jackson Memorial Laboratory. These mice belong to a tumor strain. The incidence of breast tumors in these mice at the Jackson Memorial Laboratory is about 90 per cent. It may be reduced to 8 per cent by fostering the young of high



breast tumor stock mothers to females of low breast tumor strains. The young are transferred, before they are 24 hours old. Here we cannot go into further details of this interesting phenomenon which was described by Bittner (45). We must confine ourselves to a report of therapeutic results obtained with this strain A in our laboratory during the last seven years.

During the last few years, we have also worked with breast cancers originating in mice obtained from the Rockland Farms. They do not belong to any tumor strain. They are collected from stock mice in the older age group (about 12-15

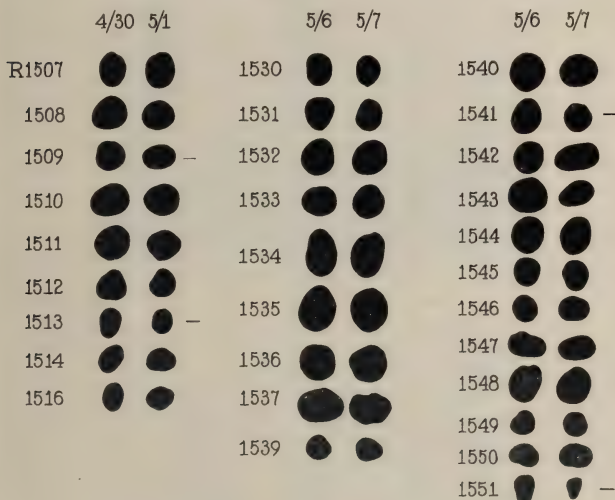


FIG. 11. Effect of simple biopsy on spontaneous breast cancers

months old). It is interesting to point out that considering the shorter life span of a mouse the age incidence of the occurrence of these tumors corresponds to 40-60 years in the life of a patient, which represents the most frequent age group for the occurrence of human cancer.

We have now had a large experience with mice from both sources (a third source used by us was the so-called Bagg Strain). In addition, we used smaller sets of Strain R 111 mice bearing the very malignant transplanted Ca 2163. Therapeutic results were identical in all these sets of mice. I have dwelt somewhat in detail on our source material as it is of some importance to show that our results were not obtained by the exclusive use of one mouse strain only.

In reviewing our work, which, as stated, extends over a period of seven years, I shall give a very brief report of our earlier work.

## SPLEEN EXTRACT

The experimental work was started with a highly concentrated spleen extract. Aqueous extracts of beef spleen containing 100 gms. of spleen per ccm. were injected subcutaneously, far away from the tumor, into mice transplanted with Sarcoma 180. Spleen extracts had been tried previously by a number of investigators, always with negative or contradictory results. They used less concentrated extracts. We found that, whereas weak extracts stimulated tumor growth, the highly concentrated extract (prepared for us by Dr. David Klein of the Wilson Laboratories), effected complete disappearance of transplanted tumors (Sarcoma 180) in 60 per cent of the animals. Spontaneous regression in controls was observed in 8 per cent only. Concentrated extracts prepared from other organs failed to show any effect on the tumors. In those tumors which disappeared subsequently, a hemorrhage appeared either immediately or within a few days. Daily injections had to be continued over a period of 4-6 weeks in order to establish complete disappearance of the tumors in 60 per cent of the animals.

Detailed description of the preparation of the spleen extracts as well as the other extracts which were used by us for therapeutic purposes were presented in our publications.

It is of interest to point out that the hemorrhages just described were not due to the Shwartzman phenomenon. This question was investigated carefully and is discussed in detail in the first paper published from our laboratory.

I would like to state that the hemorrhages, while occurring frequently in animals treated with spleen extract, were not essential for a cure. Furthermore, R. Leuchtenberger showed that early hemorrhages occur in animals treated with histamines without subsequent disappearance of the tumors.

Spleen extracts appear to be richer in these "healing substances" than extracts from other organs. This is indicated by the observation that four other organ extracts prepared identically from liver, heart, pancreas, and testis did not cause hemorrhages nor retard the growth of these tumors.

During our studies on the action of concentrated spleen extract on Sarcoma 180, a most interesting observation was made. The spleens in the healed animals grew to very large sizes, while the spleens in the controls and those resistant to treatment retained their normal size. Furthermore, mice treated with extracts from other organs showed small spleens at the post mortem examination (figs. 12 and 13).

This observation was of great importance for the progress of our problem. For it was soon found that concentrated spleen extract, while effective in transplanted tumors, when injected subcutaneously, did not act on spontaneous breast cancers. Therefore, the intravenous route was tried. However, the concentrated spleen extract, when used intravenously, caused a thrombosis of the veins and injections had to be discontinued, perhaps one of the reasons why the concentrated spleen extract did not work in spontaneous tumors.

In this connection I would like to state that while transplanted tumors responded to subcutaneous and intraperitoneal treatment, all our therapeutic work with spontaneous tumors had to be carried out intravenously. In many cases

70 or more daily intravenous treatments are required before these spontaneous tumors disappear. The injections are given into a tail vein. A perfect technique is of utmost importance, as not more than two small veins are available for treatment.



FIG. 12. (a) and (b), Spleen in animal treated with spleen extract (c) Control (Surgery, Gynecology, and Obstetrics, 1938).

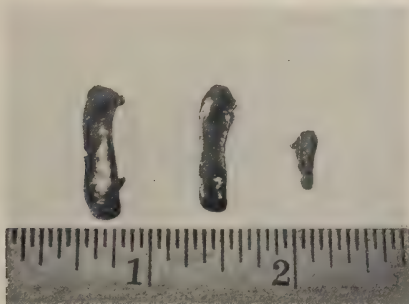


FIG. 13. (a) and (b), Spleen in animal treated with spleen extract (c) animal treated with pancreas extract. (Surgery, Gynecology, and Obstetrics, 1938.)

With an extract prepared from these enlarged spleens obtained from mice cured of Sarcoma 180, we got complete disappearance of spontaneous tumors in 30 per cent of the animals and marked reduction in size in another 30 per cent. About 40 per cent were refractory to treatment. We have been most rigid with our terminology of "healed tumor." For instance, tumors which were apparently healed clinically with completely negative palpatory findings were always

excluded from the "healed" group, when microscopic studies at the post mortem examination showed any evidence of cancer tissue.



FIG. 14. Mouse 147. J. M. L. Biopsy: Carcinoma, treatment started April 26, 1939; healed May 19, 1939; died October 3, 1939. Postmortem and microscop. exam.: no carcinoma. (Surgery, Gynecology, and Obstetrics, 1940.)

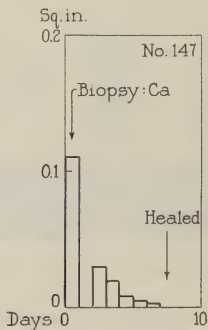


FIG. 15. Mouse 147. J. M. L. Six intravenous injections of "healed spleen" extract were given. (Surgery, Gynecology, and Obstetrics, 1940.)

The process of healing in these spontaneous tumors was entirely different from that observed in Sarcoma 180. Hemorrhages into the tumors did not occur.

The tumors became edematous, shrank gradually in size and disappeared, without leaving even scar tissue (figs. 14 and 15).

I would like to point out briefly the importance of these experiments with spontaneous tumors. Ever since methodical cancer research had been started in the early part of this century, all attempts to effect complete disappearance by an indirect route (subcutaneous, intraperitoneal or intravenous) had given negative results. Even a direct approach by excision or by radiotherapy gave results of temporary nature only. In this connection, a recent statement from the National Cancer Institute may be of interest: "On an empirical basis 977 substances and mixtures of substances were assayed for therapeutic efficacy in 18395 mice bearing transplanted or spontaneous neoplasms. No effective agent was discovered (46).

Our experimental work showed for the first time a way of effecting a cure by intravenous treatment. The extract was non-toxic. In many cases we could observe the animals for 9 months to one year in perfect health without any sign of recurrence. In a fairly small percentage (about 20-25 per cent) late recurrences were noted either locally or in other parts of the body. However, it should be noted that many of our animals belonged to a tumor strain. Probably some of these recurrences were due to too early discontinuance of treatment. It must be pointed out that these late recurrences were absolutely resistant to treatment.

The great objection to the so-called "healed spleen" extract (as we called it for want of a better name) was that, for obvious reasons, quantity production was impossible.

#### YEAST EXTRACT

In the course of our experiments with spleen extracts our attention was directed towards the possible curative rôle of certain factors of the vitamin B complex. A rich source of some of these factors and readily available in large quantities is brewer's yeast. It should be understood that brewer's yeast is not a pure strain of yeast cells, but a mixture of many ingredients obtained during the brewing process. For instance, it contains among others barley in the form of malt, hops and yeast cells.

We prepared an aqueous extract which corresponded to a concentration of 3 grams of brewer's yeast per ccm. At that time nothing was known about the action of brewer's yeast on spontaneous tumors. Maisin and his associates (47) had reported retardation of experimental cancer (induced by carcinogenic substances) in rabbits by adding boiled yeast to the food of the animals.

This extract was given intravenously in daily doses of 0.1 ccm. Attempts to treat these spontaneous tumors with yeast in powder form or in pellets were of no avail. I mention these futile attempts in order to show that we have tried again and again to substitute a simpler technique for the intravenous route and thus make it easier for other cancer research centers to repeat our experiments.

Our next step was to test various fractions of yeast extract as to their activity on spontaneous tumors. It would carry us too far to present this part of our studies in detail. In brief, the following results were obtained: The active prin-





FIG. 16. Mouse 404. J. M. L. Biopsy: Carcinoma. Treatment started December 23, 1939. Tumor healed January 16, 1940. Animal received 12 intravenous and 10 subcutaneous injections of yeast extract. Animal died November 18, 1940. Postmortem and microscopic examination: no carcinoma. No lung metastasis. Adenoma of lung. (Amer. Journal of Pathology, 1941.)

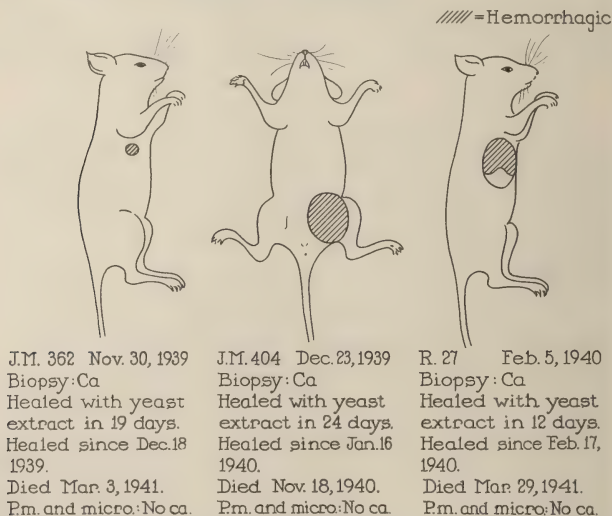


FIG. 17. Diagram of tumors in mice following injections of yeast extract. (Cancer Research, 1941.)



FIG. 18. Biopsy spontaneous mammary adenocarcinoma. J.M.L.No.314. Mag.  $\times 160$ . (Cancer Research, 1941.)

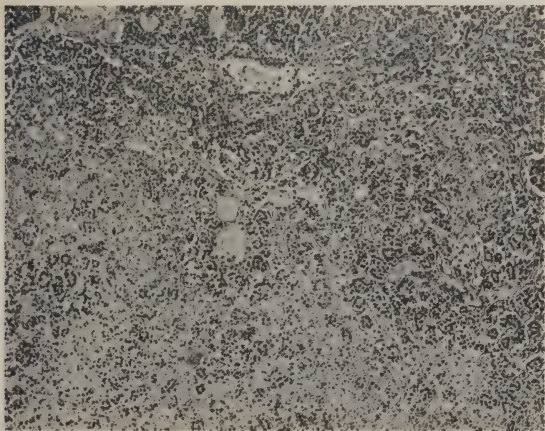


FIG. 19. Microscopic section of same tumor after 7 intravenous injections of yeast extract, showing necrosis of cells. (Cancer Research, 1941.)

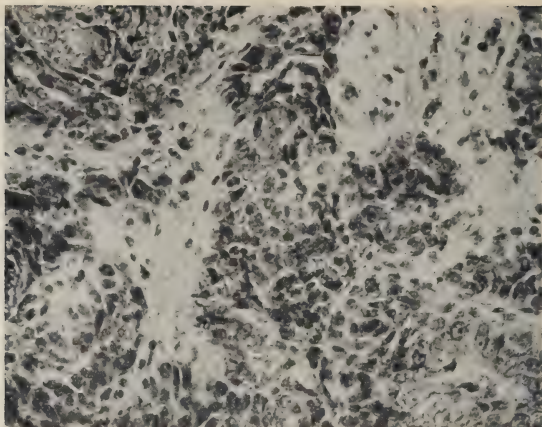


FIG. 20. Biopsy, spontaneous breast cancer in a Swiss mouse, No. 235, Rockland Farms strain. Mag.  $\times 200$ . (Cancer Research, 1941.)

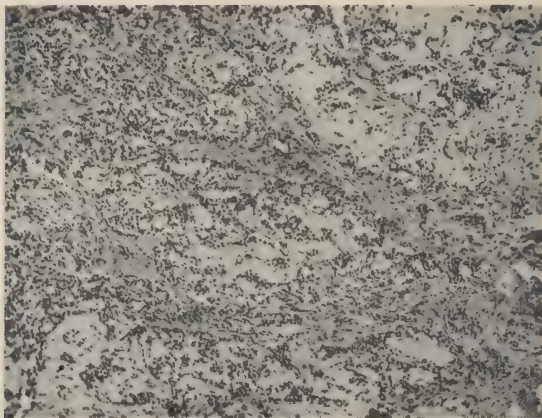


FIG. 21. Microscopic section of same tumor after 43 intravenous injections of yeast extract, showing disappearance and lymphoid change in tumor cells, lymphatic infiltration and hyalinization. Mag.  $\times 160$  (Cancer Research, 1941.)

ciple is water-soluble and comparatively thermostable at neutral pH. It is not protein in nature, not affected by nitrous acid, and is precipitated by high concentration of ethanol. The active material is not precipitated by lead acetate and silver nitrate. Active preparations can be obtained by precipitation with barium and ethanol and also by phosphotungstic acid. The active material is adsorbed by Fuller's earth and by norite, but not by permutit. Efforts at elution were unsuccessful. Autolysis of the yeast mixture prior to extraction caused loss of the active principle. Figure 16 and figure 17 show a number of spontaneous cancers healed with yeast extract.

The changes occurring in these breast cancers in mice following treatment is well illustrated in the accompanying pictures. Figure 18 shows the biopsy from

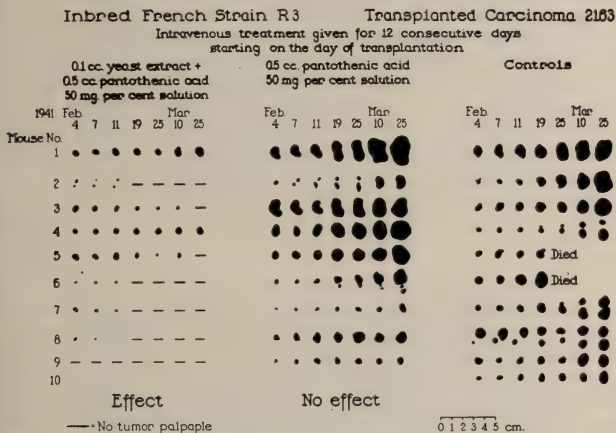


FIG. 22. Prevention of tumor growth (Science, 1941)

one of this group of tumors. Figure 19 presents the marked changes in this tumor after 7 intravenous injections of yeast extract. Figure 20 shows a specimen removed by biopsy from a breast cancer (Rockland Farms). After 43 intravenous injections of yeast extract, we see a fibrous node with partial hyalinization; small cords of lymphoid cells are imbedded in the fibrous tissue which cannot be identified any more as tumor tissue (fig. 21).

After we had worked with yeast extracts for about 18 months, we ran into unexpected difficulties. We noted that the latest results obtained with the yeast extract were far from satisfactory. These failures were due to a change in the brewing process of ordinary beer made by the brewery. We then worked with a bock beer yeast which had been prepared by the brewery according to the old formula. This yeast extract prepared from bock beer continued to give very satisfactory results, when to our dismay this source stopped completely due to



the exigencies of the war. I mention these details in order to show how many external difficulties are often encountered in research work.

#### PREVENTION OF TUMOR GROWTH

So far we have discussed the action of different extracts (spleen and yeast) in the treatment of spontaneous breast cancers in mice. A logical sequence of this work was the attempt to prevent malignant tumor growth. We used for our experiments the transplanted so-called Carcinoma 2163 in the R 111 strain, a tumor which was found to be transplantable in 95 to 100 per cent of animals of this strain. When daily intravenous injections of 0.1 ccm. of yeast extract plus 250 micrograms pantothenic acid were given for 12 consecutive days starting on the day of transplantation, 7 among 9 tumors failed to grow, whereas when 250 micrograms pantothenic acid without yeast extract were given the tumors took and grew as well as the controls (fig. 22). Further experiments along these lines showed that the vitamin B complex (pantothenic acid, riboflavin and thiamin) alone have none or very little preventive effect on tumors. Yeast alone prevents tumor occurrence in about 20 per cent only. This tumor preventing effect of yeast was markedly improved by adding pantothenic acid (non-takes 47 per cent) or riboflavin (non-takes 62 per cent) to the yeast extract. Addition of thiamin to the yeast did not improve the tumor preventing action.

Since we took up these vitamin studies and their action on cancer we were fortunate enough to have the help and assistance of members of the scientific staff of Merck & Co. I would like to express our thanks to Dr. R. Major, Dr. J. C. Keresztesy and Dr. J. Little whose cooperation and interest in our problem has been of greatest help during the last 4 years.

At the time when we had finished our experiments on tumor prevention Kensler and his associates (48) published their results on the prevention of liver cancers in rats induced by dimethylaminoazobenzene ("butter yellow"). They showed that riboflavin mixed with casein substantially protects the rat against cancers. When either riboflavin or casein alone was added to the diet, the incidence of liver cancer was reduced from 100 per cent to 70-80 per cent. When both substances were added simultaneously to the diet, the incidence of malignancy was reduced to 3 per cent.

We have pointed out repeatedly during this presentation that the percentage of cures among spontaneous tumors never went above 30 per cent, whether we used spleen extracts or yeast extracts. As attempts to raise this percentage by increasing the individual dose or by repeated daily injections failed, we considered the possibility that the diet of the animals might contain factors which antagonize our therapeutic attempts. Therefore we investigated whether a change in the diet might improve our results.

#### ACTION OF DIETS ON MALIGNANT TUMORS

Attempts to retard the growth of malignant tumors by diets are not of recent date. About 30 years ago Rous (49) presented studies on the effect of deficient diets on transplanted and spontaneous tumors.

We succeeded in improving our results when we substituted polished rice and carrot for pellets and carrots as food for the animals. The time required for a



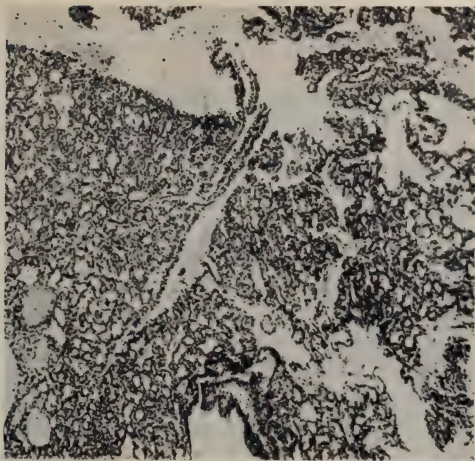


FIG. 23. Biopsy: Mammary carcinoma (Rockland Mouse No. 703) Mag.  $\times 77$  (Cancer Research, 1942.)



FIG. 24. Second biopsy, 20 days after the first biopsy. Note small rest of unchanged carcinomatous tissue. (Rockland mouse No. 703) Mag.  $\times 88$  (Cancer Research, 1942.)

cure was reduced from an average of 47 days to 20 days and larger tumors responded to treatment. In some sets we increased the percentage of complete disappearance of the tumors from 30 per cent to about 60 per cent. Another interesting observation was that hemorrhagic tumors adopted a white appearance

during the combined yeast extract-diet treatment. Sometimes within a week the hard tumor became necrotic and soft. This process is well demonstrated in figure 23 and figure 24. They represent two biopsies taken from the same tumor,

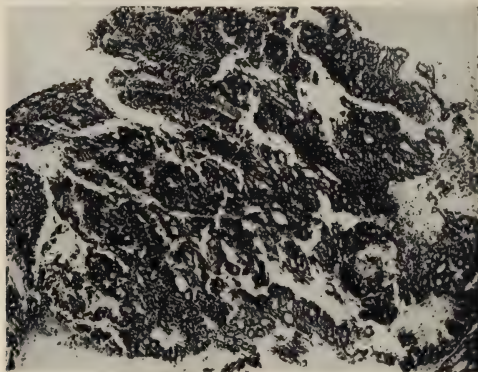


FIG. 25. Biopsy: Mammary carcinoma in Rockland mouse No. 715. Mag.  $\times 85$  (Cancer Research, 1942.)

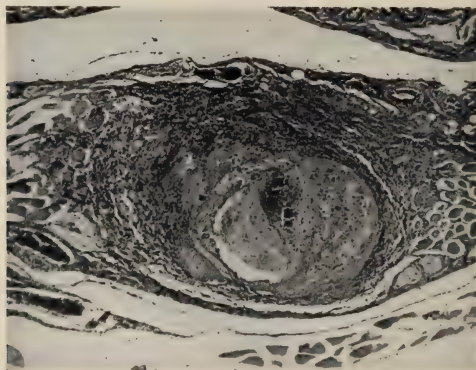


FIG. 26. Section through the site of the former tumor in mouse No. 715. Mag.  $\times 80$  Postmortem finding. (Cancer Research, 1942.)

the first before treatment was started, the other after three weeks of treatment. In another case biopsy showed a typical adenocarcinoma (fig. 25). When the mouse came to autopsy one month later, no tumor tissue could be found (fig. 26).

It is important to point out that diet alone or diet in combination with inactive yeast extracts did not show any influence on spontaneous tumors.

We observed that our therapeutic results in spontaneous tumors improved if the normal diet was replaced by a polished rice diet. The problem which confronted us at this stage was whether this improvement was due to a lack of tumor promoting substances in the polished rice or whether it contained a factor which helped actively to improve our results. The lead which aided to settle this problem was given by a series of investigations in which a bioassay test for tumor growth inhibitors was employed.

#### BIOASSAY TEST

It might be worth while to dwell for a few minutes on the practical importance of such a test for the progress of a therapeutic cancer research problem. It is conceded by most workers in this field that the supreme experimental test for any new therapeutic agent is its action on spontaneous tumors. However, it is impossible to test a large number of different fractions on spontaneous tumors for the following reasons: 1) the number of spontaneous tumors is limited, 2) a minimum of about 30 animals is necessary to allow a definite conclusion as to the activity of a fraction and 3) daily intravenous injections of these 30 animals extending over six weeks are required before a definite answer as to the value of one new fraction can be given. Thus it is plain that it would be utterly impossible to test 10 or 20 fractions simultaneously. In fact, such tests would extend over the better part of a year.

We shall describe briefly the technique of this test as it was finally developed after a great deal of preliminary work and studies.

The growth rate of Sarcoma 180 is used as an indicator and the inhibition of tumor growth is judged by comparing tumor sizes and tumor weights in treated groups with those in untreated ones. At the start of the experiment 7 to 10 days after transplantation, groups with the same number of mice are matched as to their tumor sizes (1.0 plus minus 0.2 cm. in diameter). When such matched groups are injected intravenously with saline solution twice daily for two consecutive days, the tumor sizes and weights in these mice will usually agree after a period of 48 hours. But in similar groups treated instead with extract containing tumor growth inhibitors, the tumors will fail to grow or will grow more slowly and their terminal sizes and weights will differ considerably from those of tumors in the controls groups injected with saline solution (fig. 27).

After 48 hours, the tumors are measured again and the outlines drawn. The animals are killed, the tumors are removed and their weight determined on a balance with a sensitivity of 1 mg.

It seems of importance to give two injections daily at an interval of about 12 hours. As this technique is very inconvenient (one injection has to be given either in the early morning hours or late in the evening) we attempted to determine whether one daily injection corresponding to the same daily total would be adequate. However, our experiments showed that one daily injection is not sufficient to get the desired effect.

This sketch gives the essentials of the bioassay test in brief outline. It would

| Female 'Rockland' mice transplanted with Sarcoma 180 on April 10, 1942, passage MP 15<br>Four intravenous injections (2 on April 18, 1942 and 2 on April 19, 1942)<br>with<br>Standard preparation<br>(S <sub>3</sub> ) 0.1 cc. = 5.1 mg.<br>Group 87 |                                       |  |                                      |                                       |  |                                      | Saline solution<br>0.1 cc.<br>Group 72 |  |  |
|---|---------------------------------------|--|--------------------------------------|---------------------------------------|--|--------------------------------------|--|--|--|
| Marking<br>of mice  | April 18<br>Initial size<br>(sq. in.) | April 20<br>Terminal size<br>(sq. in.) | April 20<br>Terminal weight<br>(mg.) | April 18<br>Initial size<br>(sq. in.) | April 20<br>Terminal size<br>(sq. in.) | April 20<br>Terminal weight<br>(mg.) |  |  |  |
| Front right   | ● 015                                 | ● 015                                  | 195                                  | ● 014                                 | ● 027                                  | 570                                  |  |  |  |
| Front left  | ● 015                                 | ● 016                                  | 240                                  | ● 015                                 | ● 025                                  | 600                                  |  |  |  |
| Hind right  | ● 015                                 | ● 014                                  | 190                                  | ● 015                                 | ● 023                                  | 720                                  |  |  |  |
| Hind left   | ● 017                                 | ● 023                                  | 410                                  | ● 016                                 | ● 016                                  | 320                                  |  |  |  |
| Both front  | ● 018                                 | ● 010                                  | 160                                  | ● 016                                 | ● 024                                  | 752                                  |  |  |  |
| Both hind   | ● 016                                 | ● 016                                  | 310                                  | ● 014                                 | ● 029                                  | 660                                  |  |  |  |
| Front right<br>Hind left  | ● 013                                 | ● 017                                  | 270                                  | ● 013                                 | ● 030                                  | 850                                  |  |  |  |
| Mean<br>(σ of the mean)   | 0.156<br>(0.005)                      | 0.159<br>(0.014)                       | 254<br>(32)                          | 0.147<br>(0.005)                      | 0.249<br>(0.017)                       | 639<br>(64)                          |  |  |  |

FIG. 27. Bioassay test. Effect of a "Standard Preparation" on Tumor Growth.

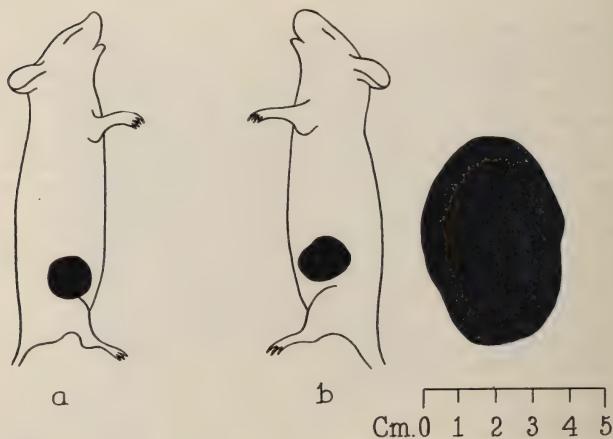


FIG. 28 (a) R. 2585. Daily intravenous injections of 5 micrograms. L. casei factor. Treatment started September 6, 1944. Tumor healed October 12, 1944, December 26th; animal living and well. No recurrence. (b) 2586 matched control. Animal died Oct. 31st, 1944. Size of tumor at death.

be impossible to discuss here finer details of the test which were published by Laszlo and Leuchtenberger in their original paper on this subject.

We have used this test extensively in our laboratory. Up to now, we have performed 1000 individual sets of experiments using about 10,000 animals. Naturally it would be impossible to give you here more than some general conclusions which resulted from these experiments.

As for the relation between inhibition of tumor growth and therapeutic action no conclusions should be drawn concerning the ultimate fate of Sarcoma 180 in treated animals, for the test is used to detect inhibitors over a period of 48 hours only. We cannot draw any definite conclusions from a positive test as to the

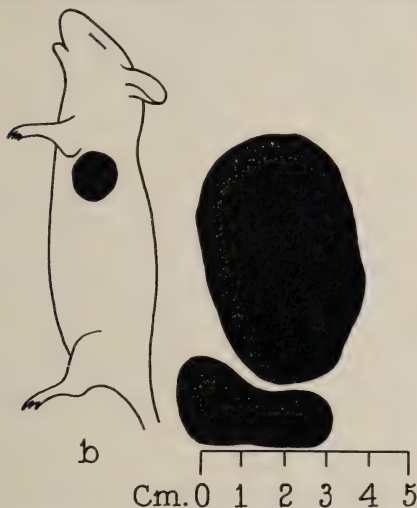


FIG. 29. R. 2615. Control. Biopsy (September 15, 1944). No treatment. Size of original tumor and new tumor on December 26, 1944.

action of an extract on spontaneous tumors. Some of the extracts and fractions that gave figures in the test practically identical with those for standard preparations, showed either a complete absence of total regressions or an incidence much lower than 30 per cent when extracts and fractions were tested on spontaneous malignant tumors. It seems important to mention that none of the various extracts and fractions that showed a negative test ever effected a complete regression of spontaneous tumors.

#### ANTICANCEROUS FACTORS IN GRAINS

In my discussion of the action of diets on malignant tumors, I raised the ques-



tion whether a lack of promoting substances or the presence of tumor active factors in the polished rice was responsible for the improvement of our therapeutic results. We attacked this problem in a series of investigations with our bioassay test. Fortunately, the effect of the polished rice diet upon tumor growth could be shown in the 48 hour period of this test. Inhibition of growth was observed with one third of the dose of the standard (yeast) extract when injected intravenously, if the animals were kept on polished rice diet instead of on a normal diet (mouse pellet). I omit to mention details of the experiments and only summarize that the presence of some specific tumor growth inhibitory factors in certain grains and not the lack of promoters was found to cause this improvement. We were able to show that the factor in polished rice was destroyed by heating. We also could demonstrate, that the feeding factor alone is unable to replace the injections of active preparations. This observation was in agreement with our failure to "heal" spontaneous breast tumors in mice with diets alone.

The presence of anticancerous factors in grains was directly proven by our success in extracting such factors from rice. These factors, in the bioassay test, acted like yeast extract, even when injected into animals, which were fed a full diet.

A number of grains were tested for the presence of the feeding factor and for the extractable factor. Barley, a rich source of both of these factors, was chosen for further trial. A set of mice bearing spontaneous malignant breast tumors in mice was injected intravenously daily with extracts of barley. The animals were fed pearled barley and carrots. This diet was given only during the period of treatment, in which the animals lost an average of five grams. After the treatment was stopped, the animals were put back on a full diet.

Our results obtained with injections of barley extract combined with feeding barley, were similar to those observed after injection of yeast extract. For instance in a series of 46 animals, 19 animals were "healed." Among 50 animals, which received no injections but the diet alone, none were healed.

#### INOSITOL

Whenever a potent source material was found, our laboratory investigated simultaneously a number of procedures. First we attempted to improve the yield of extractability of such a source. Furthermore, we tried to concentrate the active material from the crude extracts with the ultimate goal to isolate and characterize chemically the active substance or substances from the crude extracts. While such experiments with the grains were carried out systematically and quite successfully, we started a third set of investigations. We asked the question, which of the known pure chemicals would fit best into the properties of the substance occurring in our various extracts.

We had evidence suggesting that inositol or a substance related to it might have anticancerous properties. Inositol is a vitamin of the B complex and occurs in considerable quantities in our various source-materials. We tested inositol in the bioassay. The inhibition of tumor growth by inositol is well presented in table 1. It is evident from this table that the degree of inhibition depends on the dose of inositol injected. We therefore were able to use inositol in our bioassay

experiments as a standard of reference replacing crude (yeast or grain) extracts. We observed that feeding or subcutaneous injections of considerable amounts of inositol were ineffective. We also noticed that none of the 8 other crystalline B vitamins, available at the time of our investigations, inhibited tumor growth.

However, our next experiments indicated that inositol could at least not be solely responsible for the anticancerous action of our various extracts, first) though we observed definite tumor activity and complete disappearance of spontaneous tumors treated with inositol, the percentage of our successes appeared to be less than that obtained with yeast or barley extracts. Second) the amounts of inositol (as measured with bacterial assay methods) which were present in our potent extracts, were insufficient to explain the activity of the extracts on the basis of inositol alone. Finally, some of the chemical properties of our extracts differed from the chemical properties of inositol.

TABLE 1

*Effect on tumor growth of four intravenous injections of Inositol in varying doses given over a period of 48 hours\**  
(Science, 1943)

| GROUP NO. | NO. OF ANIMALS<br>IN EACH GROUP | DOSE OF INOSITOL   | MEAN TERMINAL<br>TUMOR WEIGHT | STANDARD ERROR |
|-----------|---------------------------------|--------------------|-------------------------------|----------------|
|           |                                 | γ                  | mg.                           | mg.            |
| 453       | 11                              | 0 (control:saline) | 470                           | 25.6           |
| 452       | 18                              | 38                 | 436                           | 22.8           |
| 451       | 14                              | 50                 | 350                           | 33.6           |
| 450       | 10                              | 75                 | 270                           | 34.1           |
| 449       | 7                               | 100                | 246                           | 41.1           |
| 448       | 5                               | 150                | 215                           | 26.4           |
| 447       | 5                               | 250                | 222                           | 9.8            |
| 446       | 5                               | 1000               | 142                           | 12.8           |

\* Female Rockland mice transplanted with Sarcoma 180; start of the experiment 8 days after transplantation; mice kept on polished rice diet for the experimental period of 48 hours.

#### FOLIC ACID

While our results with different extracts had been encouraging, we had been perfectly conscious of their limitations. Our ultimate goal for which we were striving for a number of years was the finding of a pure substance which would selectively damage the cancerous tissue without impairing the health of the animal.

Our studies on tumor growth inhibitors suggested the investigation of certain vitamins of the B complex and the possible importance of "folic acid" for malignant growth. We have presented conclusive evidence that inositol, a member of the vitamin B complex, inhibited tumor growth bioassay test, whereas 8 other crystalline B vitamins were ineffective.

The first step in our experimental work with "folic acid" was a careful investigation of its activity on Sarcoma 180 with the aid of the bioassay test. We tested a folic acid concentrate and the L. casei factor (folic acid). We received a folic

acid concentrate through the courtesy of Dr. John C. Keresztesy of the Research Institute of Merck & Co., Inc. and the L.casei factor from the Lederle Laboratories (courtesy of Dr. B. L. Hutchings and Dr. E. L. R. Stokstad).

In table 2 one experiment is presented in which varying doses of the "folic acid" concentrate were given, whereas table 3 shows results of one experiment

TABLE 2

*Effect on tumor growth of 4 intravenous injections of "folic acid concentrate" in varying doses given over a period of 48 hours.\* Seven animals were used in each group*

(Proc. Soc. Exper. Biol. & Med., 1944)

| GROUP NO. | DOSE OF "FOLIC ACID"† | MEAN TERMINAL TUMOR WT. | STANDARD ERROR |
|-----------|-----------------------|-------------------------|----------------|
|           | $\gamma$              | mg.                     | mg.            |
| 805       | 0                     | 951                     | 88             |
| 803       | 0.16                  | 616                     | 16             |
| 802       | 0.32                  | 566                     | 57             |
| 801       | 0.63                  | 509                     | 47             |
| 800       | 1.25                  | 470                     | 45             |
| 799       | 2.50                  | 386                     | 42             |
| 798       | 5.00                  | 333                     | 67             |

\* Female Rockland mice transplanted with Sarcoma 180; start of the experiment 8 days after transplantation; mice kept on normal diet.

† Micrograms of material of "potency" 40000 (Williams standard, as measured by *L. casei* assay.)

TABLE 3

*Effect on tumor growth of 4 intravenous injections of L. casei factor in varying doses given over a period of 48 hours.\* Seven animals were used in each group*

(Proc. Soc. Exper. Biol. & Med., 1944)

| GROUP NO. | DOSE OF L. CASEI FACTOR | MEAN TERMINAL TUMOR WT. | STANDARD ERROR |
|-----------|-------------------------|-------------------------|----------------|
|           | $\gamma$                | mg.                     | mg.            |
| 828       | 0                       | 893                     | 78             |
| 827       | 0.0063                  | 704                     | 37             |
| 826       | 0.0125                  | 650                     | 60             |
| 825       | 0.0250                  | 540                     | 23             |
| 824       | 0.0500                  | 517                     | 36             |
| 823       | 0.1000                  | 469                     | 48             |
| 822       | 0.2000                  | 394                     | 21             |
| 821       | 0.4000                  | 333                     | 18             |

\* Female Rockland mice transplanted with Sarcoma 180; start of the experiment 8 days after transplantation; mice kept on normal diet.

with *L. casei* factor. These results which were repeated in a number of tests show that these substances are strong inhibitors of tumor growth. The "folic acid" concentrate contains about 99 per cent impurities. The *L. casei* factor (Lederle) is between 70 and 80 per cent pure. It is certainly most striking that significant action on tumor cells was observed after intravenous injections of 0.16 gamma folic acid concentrate and 0.025 gamma *L. casei* factor.

At present "folic acid" is produced in minute quantities only. Thus work with these substances is limited to small experimental animals. So far we have used the intravenous route. Recently we have used intraperitoneal application. On account of the scarcity of material, we have not treated the animals with subcutaneous injections. We hope to have larger quantities of "folic acid" available in the near future.

Pollack, Taylor and Williams (50) reported that the vitamin present at the highest relative level in both human and rat cancer (the same seems to be true for the mouse) is "folic acid." They show that the inositol level is next to that of folic acid, while pyridoxine and biotin are present at relatively low levels. An interesting problem for further study would be to investigate the possible relationship between the tumor-inhibitory action of inositol and folic acid and their relatively high content in malignant tumors.

After we had tested "folic acid" in a number of experiments by means of the bioassay test and found its inhibiting action on malignant growth, we used these

TABLE 4  
*Effect of L. casei factor "folic acid" on spontaneous breast cancers in mice*  
(Science, 1945)

| NO. OF MICE | DOSE INJECTED | NO. OF HEALED TUMORS |
|-------------|---------------|----------------------|
| 60          | 5 micrograms  | 26                   |
| 60          | 0             | 0                    |
| 29          | 5 micrograms  | 12                   |

substances in spontaneous tumors. We used the *L. casei* factor ("folic acid") produced by the Lederle Laboratories. A preliminary report about our results in spontaneous tumors appeared recently in *Science* (17).

149 mice from three different strains—(Jackson Memorial Laboratory, Rockland strain and Bagg strain) bearing single spontaneous breast cancers were selected for the experiments. A definite diagnosis of malignancy was established by biopsy. The animals were kept on a normal diet (Rockland mouse pellets). 120 animals were divided into two groups (60 mice each) in such a way that they were matched as to strains and as closely as possible, as to location and size of the tumors.

One of these groups of 60 mice received daily intravenous injections of 5 micrograms *L. casei* factor over a period of 4–6 weeks; the control group of 60 mice did not receive any injections. Another set of 29 mice were also treated with 5 micrograms of *L. casei* factor, but were without "matched" controls. No toxic effect was observed in treated animals (figure 28a and b). Our therapeutic results (Dec. 26, 1944) are presented in table 4.

#### XANTHOPTERIN

In view of the scarcity of the *L. casei* factor and in view of the possible chemical relationship of folic acid to xanthopterin (the pigment of butterfly wings) (51–54) we tested the action of synthetic xanthopterin on tumor growth. In table 5 an

experiment is presented in which varying doses of xanthopterin were studied. It is evident from this table that in the bioassay test xanthopterin is a strong inhibitor of tumor growth. Similar results were obtained in 30 experiments in which 214 animals were used. In the course of investigations concerned with the substances antagonistic to tumor growth inhibitors, leukopterin was tested

TABLE 5

*Effect on tumor growth of 4 intravenous injections of xanthopterin in varying doses given over a period of 48 hours at 12 hours interval.\* Seven animals were used in each group*  
(Proc. Soc. Exper. Biol. & Med., 1944)

| GROUP NO. | DOSE OF<br>XANTHOPTERIN | MEAN TERMINAL<br>TUMOR WT. | STANDARD ERROR | SIGNIFICANCE RATIO |
|-----------|-------------------------|----------------------------|----------------|--------------------|
|           | $\gamma$                | mg.                        | mg.            |                    |
| 980       | 0                       | 866                        | 47             | —                  |
| 979       | 0.031                   | 674                        | 33             | 3.4                |
| 978       | 0.125                   | 606                        | 27             | 4.8                |
| 977       | 0.500                   | 513                        | 38             | 5.9                |
| 976       | 2.000                   | 389                        | 23             | 9.1                |

\* Female Rockland mice transplanted with Sarcoma 180; start of the experiment 8 days after transplantation; mice kept on normal diet.

TABLE 6

*Effect on tumor growth of 4 intravenous injections of xanthopterin and of a mixture of xanthopterin and leukopterin given over a period of 48 hours at 12 hours interval.\**  
*Seven animals were used in each group*  
(Proc. Soc. Exp. Biol. & Med., 1944)

| GROUP NO. | MATERIAL INJECTED          | DOSE     | MEAN<br>TERMINAL<br>TUMOR WT. | STANDARD<br>ERROR | SIGNIFICANCE RATIO |
|-----------|----------------------------|----------|-------------------------------|-------------------|--------------------|
|           |                            | $\gamma$ | mg.                           | mg.               |                    |
| 959       | Saline                     | —        | 577                           | 42                | —                  |
| 956       | Xanthopterin               | 0.5      | 341                           | 21                | to 959: 5.0        |
| 957       | Xanthopterin + Leukopterin | 0.5      |                               |                   | to 957: 5.3        |
|           |                            | 1.0      | 620                           | 48                |                    |

\* Female Rockland mice transplanted with Sarcoma 180; start of the experiment 10 days after transplantation; mice kept on normal diet.

as suggested by Dr. Keresztesy (table 6). It may be seen from this table that Leukopterin while it is no tumor growth inhibitor, neutralizes the action of xanthopterin.

When we tested the action of xanthopterin on spontaneous tumors, though results seemed encouraging in our earlier experiments, our final results were disappointing. Daily doses of 10 gamma of xanthopterin were given intravenously. These experiments must be repeated on a larger scale before final conclusions can be drawn. However, we can state here briefly that in this set 1) healing



effect was minimal; 2) many tumors after temporary regressions grew tremendously in spite of continuous treatment; and 3) many new tumors were observed among the treated animals. It is possible that changes in the individual dose may render better results.

I have presented to you a brief sketch of our work in the therapy of spontaneous breast cancers in mice. Naturally, it was utterly impossible to report in detail our successes and on the other hand many failures. A perusal of the papers which we have published will clear up many interesting points for those who are interested in this special field. Only time will tell whether our work has brought the cancer problem a step nearer to the ultimate goal of all medical research namely a successful clinical application.

#### PAPERS PUBLISHED FROM THE CANCER RESEARCH LABORATORY

1. LEWISOHN, R.: Effect of Subcutaneous Injections of Concentrated Spleen Extract on Mouse Sarcoma 180. *Surg., Gynec. & Obst.*, 66: 563, 138.
2. LEWISOHN, R., LEUCHTENBERGER, R., AND LASZLO, D.: Spleen Extract in the Treatment of Transplanted and Spontaneous Malignant Tumors in Mice. *Surg., Gynec., & Obst.*, 71: 274, 1940.
3. LEWISOHN, R., LEUCHTENBERGER, C., LEUCHTENBERGER, R., AND LASZLO, D. Effect of Intravenous Injections of Yeast Extract on Spontaneous Breast Adenocarcinomas in Mice. *Proc. Soc. Exper. Biol. & Med.* 43: 558, 1940.
4. LEWISOHN, R., LEUCHTENBERGER, C., LEUCHTENBERGER, R., AND LASZLO, D.: The Treatment of Spontaneous Breast Adenocarcinomas in Mice with Extracts of Spleen or Yeast. *Am. J. Path.* 17: 25, 1941.
5. LEWISOHN, R., LEUCHTENBERGER, C., LEUCHTENBERGER, R., AND LASZLO, D.: The Fate of Spontaneous Mammary Carcinomas in Mice after Simple Biopsy. *Cancer research*, 1: 324, 1941.
6. LEWISOHN, R., LEUCHTENBERGER, C., LEUCHTENBERGER, R., LASZLO, D., AND BLOCH, K.: Prevention of Tumor Growth (Carcinoma 2163) by Intravenous Injections of Yeast and Vitamins. *Science*, 94: 70, 1941.
7. LEUCHTENBERGER, R., AND SICHER, G.: Visceral Lesions following Single Subcutaneous Injection of Benzpyrene in Mice. *Arch. Path.*, 31: 189, 1941.
8. LEWISOHN, R., LEUCHTENBERGER, D., LEUCHTENBERGER, R., LASZLO, D., AND BLOCH, K.: Action of Yeast Extract on Transplanted and Spontaneous Malignant Tumors in Mice. *Cancer Research*, 1: 799, 1941.
9. LEWISOHN, R.: Five Years of Cancer Research. *J. Mt. Sinai Hosp.*, 8: 77, 1942.
10. LEWISOHN, R., LEUCHTENBERGER, C., LEUCHTENBERGER, R., LASZLO, D., AND DISCHE, Z.: Influence of Polished Rice Diet upon Spontaneous Mammary Cancers in Mice Treated with Yeast Extract. *Cancer Research*, 2: 818, 1942.
11. LASZLO, D., AND LEUCHTENBERGER, C.: A Rapid Test for Tumor Growth Inhibitors. *Cancer Research*, 3: 401, 1943.
12. LASZLO, D., AND LEUCHTENBERGER, C.: Inositol, A Tumor Growth Inhibitor. *Science*, 97: 515, 1943.
13. LEWISOHN, R., LASZLO, D., LEUCHTENBERGER, C., LEUCHTENBERGER, R., AND DISCHE, Z.: Presence in Various Grains of Factors Inhibiting Tumor Growth. *Proc. Soc. Exper. Biol. & Med.*, 52: 269, 1943.
14. LEWISOHN, R., LEUCHTENBERGER, C., LEUCHTENBERGER, R., LASZLO, D., AND DISCHE, Z.: Treatment of Spontaneous Breast Cancers in Mice with Pearled Barley. *Proc. Soc. Exper. Biol. & Med.*, 52: 272, 1943.
15. LEUCHTENBERGER, C., LEWISOHN, R., LASZLO, D., AND LEUCHTENBERGER, R.: "Folic Acid," a Tumor Growth Inhibitor. *Proc. Soc. Exper. Biol. & Med.*, 55: 204, 1944.

16. LEWISOHN, R., LASZLO, D., LEUCHTENBERGER, R., AND LEUCHTENBERGER, C.: The Action of Xanthoptera on Tumor Growth. *Proc. Soc. Exper. Biol. & Med.*, 56: 144, 1944.
17. LEUCHTENBERGER, R., LEUCHTENBERGER, C., LASZLO, D., AND LEWISOHN, R.: Influence of Folic Acid on Spontaneous Breast Cancers in Mice. *Science*, 101: 1945.

## OTHER REFERENCES

18. COOK, J. W., HEWETT, C. L., AND HEIGER, I.: *J. Chem. Soc. London*, 396: 1933.
19. FIESER, L. F., AND NEWMAN, M. S.: *J. Am. Chem. Soc.*, 57: 961, 1935.
20. POTT, P.: *The Chirurgical Works*, Vol. 3, p. 225, London, 1783.
21. YAMAGINA, K., AND ITCHIKAMA, K.: *Mitt. a.d. Med. Fak. Univ. Tokyo*, 15: 295 (1915): 19 (1917): 19: 483 (1918): *J. Cancer Research*, 3: 1 (1918).
22. KENNAWAY, E. L.: *J. Path. & Bact.*, 27: 233 (1924); *Brit. Med. J.*, 2: 1 (1925).  
HIEGER, I.: *Biochem. J.*, 24: 5-5 (1930).  
COOK, J. W., HIEGER, I., KENNAWAY, E. L., AND MAYNARD, W. V.: *Proc. Roy. Soc. Ser. B III*, 455, 1932.  
COOK, J. W., HEWETT, C. L., AND HIEGER, I.: *J. Chem. Soc. London*, 1933: 396.  
COOK, J. W., AND HASLEWOOD, G. A. D.: *Chem. & Indust.*, 38: 758, 1933.  
BARRY, G., COOK, J. W., HASLEWOOD, G. A. D., HEWETT, C. L., HIEGLER, I., AND KENNAWAY, E. L.: *Proc. Roy. Soc. London*, 117: 318, 1935.  
COOK, J. W., HASLEWOOD, G. A. D., HEWETT, C. L., HIEGLER, I., KENNAWAY, E. L., AND MAYNARD, W. V.: *Am. J. Cancer*, 29: 219, 1937.  
COOK, J. W., AND KENNAWAY, E. L.: *Amer. J. Cancer*, 33: 50, 1938 and 39: 51, 1940.
23. FIESER, L. F., AND SELIGMAN, A. M.: *J. Am. Chem. Soc.*, 57: 228, 942: 2174, 1935.  
FIESER, L. F., AND FIESER, M.: *J. Am. Chem. Soc.*, 57: 782, 1935.  
FIESER, L. F., FIESER, M., HERSHBERG, E. B., NEWMAN, M. S., SELIGMAN, A. M., AND SHEAR, M. J.: *Am. J. Cancer*, 29: 260, 1937.
24. ANDERVONT, H. B.: *Publ. Health Rep.*, 50: 211, 1935, 53: 1647, 1938. *J. Nat. Cancer Inst.*, 2: 139, 1941.
25. SHEAR, M. J.: *Am. J. Cancer*, 26: 322, 1936; 28: 334, 1936; 33: 499, 1938, 36: 211, 1939.  
SHEAR, M. J., LEITER, J., AND PERRAULT, A.: *J. Nat. Cancer Inst.*, 1: 303, 1940.  
SHEAR, M. J.: *J. Nat. Cancer Inst.*, 2: 99, 1941.
26. SHIMKIN, M. B., AND ANDERVONT, H. B.: *J. Nat. Cancer Inst.*, 1: 45, 1940.  
SHIMKIN, M. B., AND LEITER, J.: *J. Nat. Cancer Inst.*, 1: 241, 1940.  
SHIMKIN, M. B.: *J. Natl. Cancer Inst.*, 1: 211, 1940.
27. LEVI, A. A., AND BOYLAND, E.: *Chem. & Indust.*, 15: 446, 1938.
28. DOBRINER, A., RHOADS, C. P., AND LAVIN, G. I.: *Proc. Soc. Exper. Biol. & Med.*, 41: 27, 1939.
29. CRAMER, W., AND SIMPSON, W. L.: *Cancer Research*, 4: 601, 1944.
30. CARRUTHERS, CH., AND SUNTZEFF, V.: *Science*, 99: 245, 1944.
31. BERENBLUM, I.: *J. Path. & Bact.*, 32: 425, 1929—*Nature*, London, 136: 838, 1935.
32. HADDOW, A.: *J. Path. & Bact.*, 47: 567, 1938 and 47: 581, 1938.
33. LATHROP, A., AND LOEB, L.: *J. Cancer Research*, L; 1, 1916.
34. CORI, C.: *J. Exper. Med.*, 45: 983, 1927.
35. MURRAY, W.: *J. Cancer Research*, 12: 18, 1928.
36. LACASSAGNE, A.: *Compt. rend. Acad. des Sciences*, 195: 630, 1932.
37. LACASSAGNE, A.: *Compt. rend. Soc. de Biol.*, 114: 427, 1933.
38. GESCHICKTER, C. F., AND BYRNES, E. W.: *Arch. Path.*, 33: 334, 1942.
39. GARDNER, W. U., SMITH, G. M., STRONG, L. C., AND ALLEN, E.: *Arch. Path.*, 21: 504, 1936.
40. PYBUS, F. C., AND MILLER, E. W.: *Am. J. Cancer*, 34: 348, 1938.
41. LACASSAGNE, A.: *Compt. rend. Soc. de Biol.*, 126: 193, 1938.
42. GARDNER, W. U.: *Yale J. Biol. & Med.*, 12: 544, 1940.
43. NATHANSON, I. T., AND ANDERVONT, H. B.: *Proc. Soc. Exper. Biol. & Med.*, 40: 42, 1939.

44. LACASSAGNE, A.: Bull. Assoc. Franc.: Pour L'Étude du Cancer, 271: 1, 1938.
45. BITTNER, J.: Proc. Soc. Exper. Biol. & Med., 45: 805, 1940.
46. TURNER, F. C.: Nat. Cancer Inst., 4: 249, 1943.
47. MAISIN, J., POURBAIN, Y., AND CACYMAEX, P.: Comptes rendus, Soc. Biol. Paris, 127: 1477, 1938.
48. KENSLE, C. J., SUGIURA, K., YOUNG, N. F., HALTER, C. R., AND RHOADS, C. P.: Science, 93: 308, 1941.
49. ROUS, P. J.: J. Exper. Med., 20: 433, 1914.
50. POLLACK, M. A., TAYLOR, A., AND WILLIAMS, R. J.: University of Texas Publication, 56: 4237, 1942.
51. MITCHELL, H. K.: Science, 97: 442, 1943.
52. TOTTER, J. R., AND DAY, P. L.: J. Biol. Chem., 147: 257, 1943.
53. TOTTER, J. R., SHUKERS, C. F., HOLSON, J., RIMS, V., AND DAY, P. L.: J. Biol. Chem., 152: 147, 1944.
54. WRIGHT, L. D., AND WELCH, A. D.: Science, 98: 179, 1943.

# TIBIAL RE-IMPLANTATION FOR OSTEOMYELITIS<sup>1</sup>

## (A MODIFIED ORELL PROCEDURE)

ROBERT K. LIPPMANN, M.D.

Although sulfa drugs and penicillin have profoundly influenced the course of acute staphylococcus aureus osteomyelitis, chronic diffuse diaphysitis is still encountered as a residuum with surprising frequency. Inadequate dosage, resistant organisms and inaccessibility of the drug to the involved bone are probably causative factors. Otologists have called attention to the "masking" effect of sulfone therapy in otitis (2) and it seems likely that the diffuse indolent spreads of infection under consideration represent the result of an equivalent process. In any event, these cases possess all the inconvenience and hazard that characterizes chronic osteomyelitis and accordingly merit radical therapy.

Only surgery that removes all infected bone tissue can hope to accomplish cure in wide-spread osteomyelitis and total diaphysectomy has been often employed with this objective. This operation is now discredited, however, because of the frequency of failure of regeneration, particularly in adults, an eventuality which calls for amputation. Moreover, when regeneration does occur, the resulting bone is frequently so shortened that a disabling discrepancy in length occurs (1, 3, 6).

Various grafting procedures have been proposed to stimulate osteogenesis after diaphysectomy with the object of diminishing the incidence of these unfortunate results. Of these procedures, the ingenious plan of Orell (5) appears most capable of successful development. After diaphysectomy, Orell recommended boiling the removed bone until sterile and replacing it in its original bed. A dead but autogenous and perfectly fitting graft is so utilized to retain the normal bone length, to provide a non-irritating framework upon which new living bone may be deposited and to provide a local deposition of bone salts to be utilized for the calcification of the new osteoid tissue. Orell's method has yielded promising results in uninfected cases such as neoplasms. In osteomyelitis, however, the replacement of a sterilized graft into its chronically infected bed results too often in its prompt re-infection and ultimate sequestration—a result identical with that after simple diaphysectomy.

In the hope of overcoming this eventuality a surgical plan was developed along the following line of thought. The original spread of infection in these cases occurs during the administration of sulfone therapy. In part, at least, this original failure of the drug would seem attributable to its inaccessibility to the diseased bone because of obliterated vascular channels. After grafting, sulfone drugs administered by mouth would appear to be still more inaccessible to the graft because of its greater isolation from the general circulation by the operative procedure. On the other hand, a concentrated local reservoir of sulfathiazole deposited in the graft proper after its sterilization, should dissolve slowly in the

<sup>1</sup>From the Orthopedic Service of The Mount Sinai Hospital.

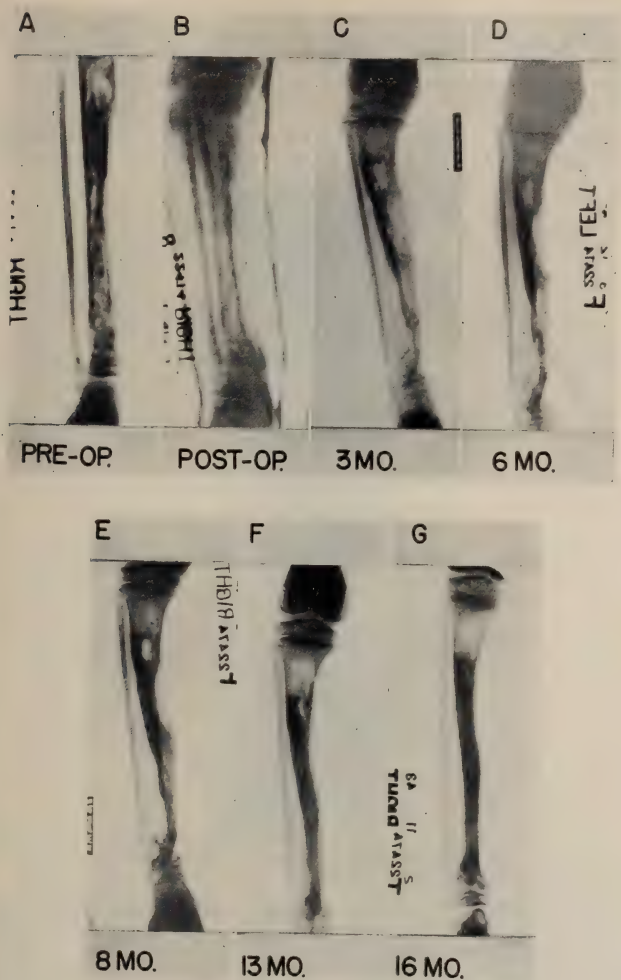


FIG. 1. X-ray survey of progress of bone replacement.



local tissue fluids, continually bathing the graft and its immediate surrounding structures with the drug. Moreover, it appeared reasonable that a deposit so isolated from the circulation should persist for a considerable length of time.

The case herewith presented was operated upon according to these considerations.

*History:* G. S. (Adm. 22474), male, aged 6 years, entered The Mount Sinai Hospital September 2, 1941, with the history of having developed an infection in an abrasion on the right

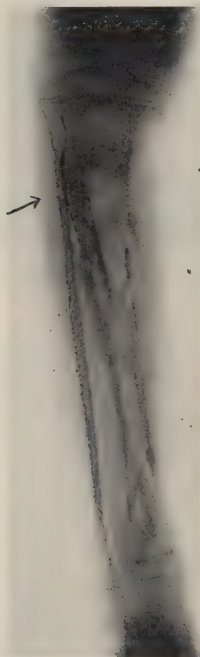


FIG. 2. Six weeks post-operatively. Firm callus can be already visualized extending from the upper viable fragment to about the upper end of the graft.

leg three weeks previously. Severe pain developed in the shaft of the right tibia originating at the upper angle but gradually involving the entire bone. Treatment by his family physician was said to have included the use of sulfone medication which appeared to reduce temperature and pain. Two weeks before admission, however, the temperature rose to 102°F. and was followed by the spontaneous discharge of a large quantity of thick yellow pus. Temperature and pain dropped promptly but soon rose again so that for the week preceding admission the temperature maintained a level of approximately 101°F.

*Examination:* On admission the child complained of severe pain in his right leg below the knee. His temperature was 103°F. He was moderately emaciated but did not appear acutely ill. There was marked tenderness and swelling of the right leg below the knee. Two central fistulae discharged thick pus when pressure was applied to the surrounding soft tissues. Wound cultures consistently revealed staphylococcus aureus in pure culture. There was no clinical evidence of sepsis and several blood culture studies yielded no organisms. Tenderness was marked and corresponded to the entire shaft of the tibia. X-rays disclosed an extensive osteomyelitis involving the entire shaft of the bone (fig. 1A).

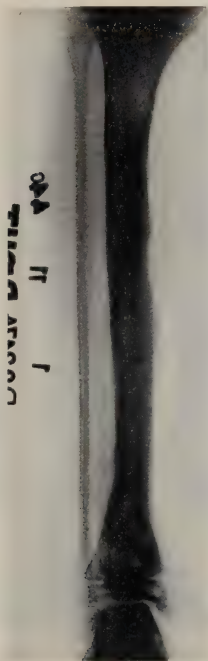


FIG. 3. X-ray showing restitution two years and three months after operation.

*Course:* In the weeks following admission, the temperature rose to the level of 102°F. every day despite the institution of intensive chemotherapy with various sulfone derivatives, plaster immobilization as well as general supportive therapy.

*Operation:* Five weeks after admission on October 8, 1941, under gas-oxygen-ether anesthesia, radical operation was performed. Under tourniquet hemostasis a longitudinal incision was made—epiphysis to epiphysis adjoining the tibial crest over the dorsiflexor muscle group. The upper and lower epiphyseal lines were identified and the intervening shaft of the tibia separated by subperiosteal dissection. One-quarter inch central to both

epiphyses, the bone was transversely sectioned with an osteotome so freeing the entire shaft which was then removed and boiled for twenty minutes. While the shaft was boiling, its periosteal bed was packed solidly with sulfathiazole powder, a considerable amount of which was permitted to remain when the graft was replaced into its bed. Although sequestrum and involucrum could have been easily identified and separated, the entire structure was used in toto. Closure was by catgut periosteal suture, silk skin suture and a circular plaster of Paris mid-thigh to toes. A transfusion was given on the day of operation and on the following day.



FIG. 4. Present appearance of involved extremity.

*Post-operative:* The day after operation, the patient's temperature rose to 102°F. for several hours. After this, and for the entire period of convalescence, the temperature failed to rise above 100°F. The post-operative course was entirely uneventful. Treatment during this phase consisted of changes of plaster at approximately six weekly intervals. Small fistulae were generally encountered during these changes of plaster which discharged small sequestrae and then healed. Occasionally, superficial sequestrae were sought after with a forceps and extracted and on one occasion a small incision was made for the same purpose (April 1, 1942).

Progress in recalcification was remarkably steady (fig. 1). At six weeks after operation,

circumferential callus was already visible about the graft ends (fig. 2). Four months after operation a walking plaster and iron were applied and weight bearing instituted. Two months later this was changed for a brace which was worn for several months. Occasional small sequestrae continued to extrude at steadily growing intervals, the last in May, 1943. The last x-ray taken in January, 1944, revealed excellent reconstitution of the tibial shaft with a well formed marrow cavity and no residual evidence of osteomyelitis (fig. 3).

At the time of his last examination, June, 1944, complete restitution had been attained—no symptoms, normal gait, no bowing, leg lengths equal. Knee and ankle joints permitted normal motion (fig. 4).

#### DISCUSSION

In evaluating the above procedure, it is important to remember that, at the age of six, bone regeneration often follows simple diaphysectomy. It is therefore necessary to inquire whether in this case anything has been contributed by the dead graft since it cannot carry living osteoblasts.

While surgeons prefer viable to dead grafts, they have been repeatedly surprised at the extent to which the results of dead grafting approximate those following the use of live bone. Since dead bone cannot possess osteoblastic activity, its value must be attributable to the other factors that have been enumerated. In this instance, has the graft fulfilled these functions?

1. The prevention of longitudinal collapse by serving as a strut between the bone ends.

Equal leg length in this patient after regeneration indicates that this objective has been fulfilled.

2. The preservation of space of ample cross section between the bone ends within which callus may grow.

This factor may well be the most important element contributed by the dead graft and may be likened to the hematoma following fresh fractures which provides a culture medium into which fibroblasts may grow. If collapse of the periosteal wall is permitted to occur and the space originally occupied by the bone so obliterated, it may be replaced by a thin avascular fibrous cord, an unsuitable nidus for the development of a new bony shaft. The X-rays show that in this case, the replaced bone has preserved ample space from fibrotic organization.

3. The provision of a non-irritating local source of bone salts and a framework upon which new bone may grow.

That these are not entirely theoretical considerations is evidenced by the rapidity with which the replaced graft became firmly anchored by callus extending from the viable bone above and below and by the speed with which the new shaft developed—a speed considerably greater than that following successful cases of simple diaphysectomy.

4. That the graft was non-irritating and did not act as a foreign body is evidenced by the absence of post-operative reaction, by its failure to be extruded en masse as a foreign body and by the X-ray evidence of rapid callus growth about its limits.

By these criteria it is reasonable to conclude that in this case the graft was useful if not essential for the development of the new bone shaft. The ultimate

utility of this operative procedure in osteomyelitis remains to be determined by further experience. It is particularly important to determine whether non-viable autogenous grafting can be trusted to insure the formation of a new shaft in older patients, since in adults, diaphysectomy generally is followed by failure of regeneration.

#### SUMMARY

Attention is called to the continued occurrence of indolent spreads of bone infection in spite of the use of chemotherapy—possibly because of inadequate dosage. In the case herewith reported a modified Orell operation augmented by local sulfone deposition was successfully employed in a child of six for the treatment of extensive tibial metaphysitis. Until a larger experience has accumulated, it is necessary to be extremely guarded in evaluating the applicability of this method to older patients in whom spontaneous regeneration is more faulty.

#### BIBLIOGRAPHY

1. BOSWORTH, D.: J. A. M. A., 101: 20, 1542, 1933.
2. MAYBAUM, J.: J. A. M. A., 112: 2589, 1939.
3. NICHOLS, E. H.: Acute, sub-acute and chronic infectious osteomyelitis. J. A. M. A., 42: 439, 1904.
4. OLLIER, L.: La Regeneration des Os, Paris. V. Masson et Fils. 1867.
5. ORELL, S.: Bone & Joint Surg., 19: 813, 1937.
6. PREMISTER, D. B.: Discussion. J. A. M. A., 101: 20, 1545, 1915.



## PULMONARY EMPHYSEMA

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In this communication we wish to submit certain considerations for a new interpretation of pulmonary emphysema, in all its aspects. Our concept about the nature, pathogenesis and etiology of pulmonary emphysema offers a logical way out of the confusion which prevails as regards the beliefs now held about this disease and particularly about its diagnosis.

We are in the embarrassing situation that the diagnosis of pulmonary emphysema is now shrouded in a cloud of skepticism. This at a time when the need for its early recognition is becoming more important than ever.

Pulmonary emphysema has become one of the most common clinical conditions. Our studies of the past five years have convinced us that there has occurred recently a marked increase in the incidence of this disease. For reasons which will be discussed below, it is generally overlooked and undiagnosed until late in the disease.

The timeliness for a rediscussion now of pulmonary emphysema should be obvious. The place for this discussion, we feel, is particularly proper in this volume dedicated to Dr. Eli Moschcowitz who has made distinguished contributions to our knowledge of this subject in his pioneer work on pulmonary hypertension.

*Recent Rise in the incidence.* It is a matter of clinical experience that the incidence of pulmonary emphysema is increasing. From our experience and study of this disease for the past five years we have reached the following conclusions. Two new factors have probably been added recently to those long associated with the origin of emphysema:

1. The rising incidence of heart disease in the middle aged population.
2. Chronic mild lung injury due to occupational exposures in modern industry.

Ad 1) Of the greater number of people now reaching middle age, many suffer from emphysema. This is not however the symptomless emphysema of the senile lung but rather that complicating chronic cardiac disease. It is a well established fact that the incidence of chronic cardiac disease has vastly increased recently because of the increased number of middle aged people now living. Our observations indicate that *pulmonary emphysema is often the first clinical indication of slowly progressive heart failure*. This is often overlooked in these middle aged cardiacs.

Ad 2) Modern industry has brought about occupational exposure to dusts, vapors and fumes. More workers are now so exposed and the chronic lung injury manifests itself later chiefly in the early and insidious development of emphysema. This in turn creates marked predisposition towards chronic bronchopulmonary infections complicating the emphysema which is mostly overlooked.

*The present skepticism regarding diagnosis.* Pathologists have long ago noted

the great discrepancy between the clinical signs of pulmonary emphysema and its postmortem evidence. Cabot (1) showed the extent of this discrepancy by the truly disillusioning figures obtained at the Massachusetts General Hospital. Of 12 cases diagnosed as pulmonary emphysema, only three showed postmortem evidence of it, while of 153 cases recognized postmortem as pulmonary emphysema, only seven had been so diagnosed clinically. In the face of these facts Cabot gave up as hopeless the clinical diagnosis of pulmonary emphysema.

More recently, in his Goulstorian lectures, Christie (2) comments bluntly on the same note of hopeless skepticism. Reporting an analysis of 72 cases studied postmortem he states: "The only conclusion that can be drawn from these series of cases is that the signs of emphysema are unreliable; they may be absent in patients suffering from the disease, and are not uncommonly present in patients without emphysema."

He believes that "It is those with little clinical experience who think they have a clear conception of the diagnosis of emphysema."

*The reasons for skepticism:* Two basic misunderstandings cause the present confusion about emphysema:

1. It is usually taken for granted that "structural emphysema" and "clinical emphysema" are identical and coterminous. In fact these are two distinct though related conditions.

2. Pulmonary emphysema is generally looked upon as a distinct clinicopathologic entity. In fact however, emphysema of the lungs never exists by itself; it is always but a secondary manifestation resulting from some other primary condition of the lungs, heart or chest.

Ad 1) The signs and symptoms of clinical emphysema are those of the functional involvement of the lungs as a whole. The postmortem evidence of "structural emphysema" is a topical change of the organ such as bullous distention of air-spaces and associated fibrosis.

Ad 2) The primary pulmonary or cardiac condition of which emphysema is but a complication or sequelum, often dominates the clinical picture, particularly in the preterminal phase. Not only is clinical emphysema often overlooked, but also structural emphysema of lesser extent is frequently unseen even at postmortem.

These facts will explain the great discrepancy between postmortem findings and the clinical signs and symptoms of pulmonary emphysema provided the concepts "functional emphysema" and "structural emphysema" and their interrelation in the features of clinical emphysema are properly understood.

The following should serve to elucidate this point:

### The biology of emphysema

In its present usage the term emphysema implies broadly the increased volume of the lungs. The term indicates a condition of the lungs in which two distinct components are to be considered:

1. Increased lung volume due to increased number of airspaces normally expanded.

## 2. Increased lung volume due to abnormal overdistention of airspaces.

The latter is a permanent structural change while the former is a functional condition which may or may not be reversible.

These are often spoken of as two distinct forms, namely, the so-called compensatory and "structural" emphysema. Theoretically speaking, this is perhaps correct, but in reference to "clinical emphysema" this distinction is incorrect. *The two conditions are clinically indistinguishable component parts of emphysema: also they are pathogenetically inseparable.* "Clinical emphysema" is neither exclusively compensatory nor exclusively structural emphysema. It rather consists of a combination of the two in proportions of very wide range depending on the primary clinicopathologic process in the lungs and the rate of its progress.

Emphysema develops and progresses as involved areas of the lungs stop functioning, and the unaffected remaining parts assume the burden of compensation. It is conceivable that all lobes of the lungs have large reserves of available lung units which are not constantly utilized for function while at rest (Miller and Rappaport(4)). An increasing loss of lung tissue results in utilization of the reserve lung tissue for expansion and increased function. This is compensation. Prerequisite to such efficient compensation is an ample reserve of intact lung units. Here enhanced intrinsic function increases the partitioning within the airspaces, and affords added breathing surface, without encroaching on the space in the chest. In the pathologically involved lung units where intrinsic function is affected, compensatory increased chest traction will only effect progressive disappearance of the partitions and coalescence of airspaces into bullae of variable size. This results not only in further decrease of breathing surface but increases the need for compensatory function and expansion of all available airspace. Thus the need for ever more space in the chest rises while at the same time the power to retract is being lost in an increasingly greater number of spaces transformed into bullae.

In this manner of development and progress clinical emphysema embraces all stages of lung function from compensation to decompensation in a logical sequence of pathogenetic events.

1. *Reversible functional emphysema* is present in the quasi subnormal "effort lung," in excessive sport exertions, mountain climbing, etc. It is not generally appreciated that this apparently normal condition is commonly present *during hard labor* particularly when carried in excess of individual fitness. The latter may perhaps be even regarded as a transition between the normal and the clinical manifestation of emphysema. A similar degree of emphysema occurs in all forms of acute and widespread alveolitis. Such as encountered in acute broncho-pneumonia, miliary lesions of influenza, tuberculosis, and during the asthmatic paroxysm.

In these conditions the volume of the lungs as a whole is increased for the duration of the acute process, subsiding before permanent structural changes have been produced.

2. *Irreversible functional emphysema* implies that the need for compensatory hyperfunction is constant throughout life because the lost lung units can no

longer be recovered. The volume of the lungs as a whole is permanently enlarged, because of the need for keeping an increased number of units permanently expanded to augment the function of the lung. The need exists of course only in vivo and vanishes as life and power to maintain overexpanded chest capacity ebbs away. It lies in the nature of the aforesaid pathogenetic process that irreversible emphysema will invariably be associated with and enhances the production of more or less extensive structural changes. Not only do the two coexist, but the transition from functional to structural emphysema in the same lungs is imperceptibly fluent.

3. *Structural emphysema* is the final phase in the pathogenetic process whereby the airspaces are coalesced into bullous structures of variable size. The loss of breathing surface is in direct proportion with this process and this loss must be compensated for promptly by functional emphysema, i.e., expansion of all available reserve units. Eventually of course, progressively increasing structural changes, i.e., bullous distention of affected units will reduce the available reserve of lung units as well as encroach upon the limited space available in the chest. Thus a limit will be set for the extent of functional emphysema feasible.

*Pathogenesis of "clinical emphysema."* Irreversible functional emphysema and structural emphysema combined in variable proportions constitute the condition we recognize clinically as emphysema of the lungs. Often the functional component is markedly out of proportion to the small extent of structural change and vice versa. Marked degrees of structural emphysema are often present with but slight functional disturbance. Similarly the lung volume increase is most variable. The range fluctuates, with extreme pulmonary distention in some cases, while in others the volume of the lung is hardly above normal. Particularly structural changes of marked degree (giant bullae) may exist in the lung without increasing the volume of the lung as a whole (so called senile emphysema, pneumatocele, cystic lung).

*Functional emphysema* is more likely to increase the volume of the lungs, although this increase is often cancelled out by the reduction in airspace resulting from the primary affection. When "clinical emphysema" is associated with great increase in lung volume we are mostly dealing with a predominance of the functional component in which dysfunction of the bronchi plays an important rôle. So called spasm of the finer bronchi and the obstructive element which this introduces into the picture of emphysema has been recognized for over a century and has always loomed large in the minds of observers trying to explain emphysema.

The other mechanical factor often considered in the pathogenesis of emphysema is distention by increased negative intrathoracic pressure.

Most recently Gordon (3) argued rather impressively for the simultaneous action of mechanical obstruction and distention in the pathogenesis of emphysema.

As explained above, we believe compensatory expansion of airspaces in emphysema is not produced by extraneous mechanical forces but rather by

intrinsic physiologic reflexes. Functional emphysema is the result of a reflex which may be elicited from anywhere in the entire thoracopulmonary apparatus including the bronchi.

There is evidence that in the emphysematous lung the bronchi and bronchioles have a tendency to be dilated. We know little about the condition of the finest intercalating airpassages. As these lack cartilaginous enforcement, they are likely to be stretched and perhaps narrowed in the over-expanded lung. Increased reflex tonicity of the myoelastic elements of these airpassages acts not so much as a lumen obstruction but rather as an obstruction to mobility which is normally greatest just at this point of the airways. Here is the bottleneck in the ventilatory mechanism which as is well known is disturbed in emphysema because of immobilization of the organ. All of this is however clearly the effect and not the cause of emphysema.

Even Christie, who most recently (Goulstanian lectures 1944) and with great skill once more resumed the argument in favor of the obstructive theory, had to concede that clinical observations are hard to reconcile with it. As he puts it "some patients with chronic bronchitis or asthma develop emphysema comparatively rapidly while others never become emphysematous."

It has been our observation that in cases where chronic asthma or chronic bronchitis and their combinations have resulted in clinical emphysema, lack of pulmonary reserve preexisted or developed by progressive fibrosis and destruction of lung tissue because of complicating recurrent pneumonitic processes in childhood or early adult life.

Our observations taught us that in most cases of chronic bronchitis secondary to persistent suppuration in the upper respiratory tract, emphysema remains functional and in the reversible stage for a great number of years, until suppurative pneumonitis supervenes leaving extensive areas of pulmonary fibrosis in which bronchiectatic changes have developed. Even then the patient with almost incessant cough and expectoration will have only functional emphysema which is now however permanent (irreversible). Only when these patients reach advanced age will there be found some structural emphysema which is not produced by these symptoms. It is likely to be exaggerated into bullae in the presence of severe bronchitic complications.

On the other hand development of emphysema is commonly observed to progress fairly rapidly from the functional reversible to the irreversible and the marked structural emphysema stage with little if any bronchitic complications.

Thus clinical pathological observations bear out the inferences to be drawn from necropsy findings that emphysema complicating chronic bronchitis is more apt to be functional while true structural emphysema is less likely to be complicated by severe bronchitic changes.

*The discrepancy between clinical and necropsy findings.* In the light of the foregoing we can readily explain the much discussed discrepancy between the clinical and necropsy findings.

Clinicians are apt to overlook cases of predominant structural emphysema at least until this becomes complicated by bronchitis, where the added func-



tional emphysema draws attention to the condition. That marked structural emphysema often exists for many years without complicating bronchitis and functional emphysema, is evinced by the fact, complained of by pathologists, that emphysema is often overlooked by clinicians and first revealed at necropsy.

Pathologists, in turn, are apt to overlook predominant "functional emphysema" which is often the chief cause of death in patients with little structural emphysema when complicated by severe bronchitic changes. Most of the evidence of even fatal emphysema irreversible in life will escape the pathologist who so often fails to find emphysema diagnosed by the clinician. Also clinically marked degrees of emphysema aggravated by severe bronchitic changes may persist for many years without producing structural emphysema of more than mild extent.

#### THE ETIOLOGY OF PULMONARY EMPHYSEMA

As pointed out before, pulmonary emphysema is not a primary disease but a sequela to a great variety of conditions affecting the lungs, the chest or the heart. The origins of emphysema must therefore be retraced into the past history of the individual in every instance.

The natural history of this disease calls for the broadest type of etiologic study. In making such an investigation in all our cases observed during the past 5 years, we have been led to the following concepts of the etiology.

Every case represents the end of a disease cycle. The first stage in this cycle is a substandard pulmonary or thoracic apparatus, which is either brought along with birth (congenital), acquired in early life (damaged postnatal growth) or acquired in later life. Upon the basis of the organ predisposition thus created, the emphysematous process in the lungs is set off by one of the common pulmonary affections. The cycle is finally closed by disturbances in pulmonary circulation brought about in later life with weakening of the cardiocirculatory functions.

In clinical terms we may thus distinguish 3 groups of factors in the etiology of pulmonary emphysema. They are as follows:

1. Predisposing factors:
  - a. Maldevelopment of the lungs
  - b. Chest deformities
2. Chronic pulmonary diseases resulting in loss of parenchyma by fibrosis or destruction
3. Disturbances in pulmonary circulation.

1. *Predisposing factors* include congenital and acquired inadequacy of the lungs, as implied particularly in hypoplasia, i.e., damaged postnatal growth of the lungs by childhood involvement of the organ. Chest deformities include not only congenital and acquired kyphoscoliosis but also those acquired in late life by obesity, senility, faulty posture or arthritic changes.

2. *Chronic pulmonary affections*, are primarily caused by recurrent pneumonic and bronchitic infections. These are often the complications of respiratory tract allergy, but even more often these represent bronchopulmonary suppurative disease of a primary nature. Pulmonary fibrosis resulting

from chronic granulomas, mycoses, pneumoconiosis or other chemical and physical lung irritants, form a large part of the great bulk of conditions in the second group.

3. *Disturbances in pulmonary circulation* include three types:

a. *Passive congestion*. This may be acute as in cardiac asthma or chronic as in rheumatic and arteriosclerotic heart disease.

b. *Active hyperemic congestion* as produced by hard labor or sport in excess of fitness or by alcoholism.

c. *Pulmonary vascular disease*. Includes thromboembolism with infarction, primary pulmonary arteriosclerosis, congenital cardiac disease.

Our etiologic studies indicate that development of early (presenile) emphysema is precipitated by loss of breathing surface due to primary pulmonary diseases or to occupational exposure to the inhalation of harmful substances. More often pulmonary emphysema develops only during or past middle age and is then brought on by insidiously progressive weakening of cardiovascular function.

Thus the illness which terminates in cardiopulmonary decompensation resulting from emphysema starts in early life with relative pulmonary insufficiency, it progresses with complicating infections during late years and is often brought to completion by the weakening heart in middle life.

Chronic hypertensive and arteriosclerotic heart disease is particularly very common in the middle aged working population. We were surprised to find that in spite of the large proportion of industrial cases in our material the etiologic significance of the cardiocirculatory factor appeared to play a rôle equally important with that played by lung damage from industrial exposures.

This will explain the order of incidence of *factor-combinations* as listed on the table based on material made up of clinical and industrial cases in about equal proportions. It should also be noted that in the type of patient we were dealing with, hard labor in excess of the capacity restricted by early pulmonary and subsequent cardiocirculatory limitations loomed so large that it contributed apparently to almost every group of factor combinations.

#### ETIOLOGIC FACTOR-COMBINATIONS IN ORDER OF INCIDENCE

1. Malformation of lungs or deformity of chest combined with recurrent infections

Alone or with

Hard labor or alcoholism—early emphysema. Arteriosclerotic changes—late emphysema

2. Respiratory tract allergy combined with recurrent infection (pneumonitis)

Alone or with

Hard labor or alcoholism—early emphysema. Arteriosclerotic changes—late emphysema

3. Chronic passive congestion (rheumatic or luetic heart disease)

## With

Recurrent infections or hard labor or alcoholism—early emphysema

4. Occupational lung damage (pneumoconiosis etc., pulmonary fibrosis)

## Alone or with

Complicating infections or hard labor or alcoholism—early emphysema.

Arteriosclerotic changes—late emphysema

5. Old Tuberculous fibrosis plus recurrent infections

## Alone or with

Hard labor or alcoholism—early emphysema. Arteriosclerotic changes—late emphysema

6. Postural chest deformity (obesity, senile skeletal changes)

Combined with recurrent infections and arteriosclerotic changes—late emphysema

## DIAGNOSTIC FEATURES OF CLINICAL EMPHYSEMA

As mentioned before there prevails general skepticism as regards reliability of our diagnostic criteria of emphysema. From our experience we are convinced that the classical criteria as handed down to us from Laennec to Osler are still adequate for the diagnosis of this condition particularly when amplified by recently recognized clinical and x-ray features.

*Great variability in the clinical features* of emphysema is just what we should expect in the light of the foregoing.

Functional emphysema will manifest itself chiefly by physical signs while structural emphysema will be demonstrable chiefly by x-ray features. Since the bulk of clinical emphysema represents a combination of functional and structural emphysema, our diagnosis must rest on the combination of physical signs plus x-ray evidence.

Symptoms of cough, insidious progressive dyspnea and cyanosis are commonly seen as emphysema progresses.

The most significant feature is overdistention of the lungs indicative of "increased need for space" in the organ. The direction of this overdistention differs according to constitutional chest type and localization of preceding pathology. Our experience leads us to distinguish four main types as follows:

1. Forward distending—soldierly bearing type
2. Downward " long flat chest "
3. Upward " round shoulder "
4. Roundly " barrel chest "

Transitions between or cross types are quite frequent but predominance of one over the other type is sufficiently distinct for classification. Individuals of asthenic constitutional type with long narrow chest when developing emphysema are more likely to distend their chests in the forward or downward direction, i.e., taking forms 1 or 2. Individuals of the sthenic or hypersthenic

constitutional type are more apt to distend their chest in emphysema in upward or all round direction taking forms 3 or 4. The extent of deepening as well as lengthening the chest cavity must be evaluated in reference to body build.

The physical signs in order of their significance:

1. *Chest fixation*: It begins with restricted motion in the main direction of overdistention ending up eventually in restricted en masse movement of the chest (as a whole) with every breath.

2. *Prolongation of breath sounds* with progressive diminution in intensity over the distended fixed parts particularly.

3. *Wheezing, sibilation*, (rhonchi) dry and moist.

4. *Increased percussion resonance* of chest over the distended areas.

5. *Variability of physical signs*. Upon forced breathing or coughing dullness changes to hyperresonance and breathsounds become muffled over areas where they were well audible previously.

6. *Differences in timing of breathsounds and rales* are noted over different lung areas. Breathsounds are not synchronous over the chest; expiration may be heard over one part of chest while inspiration is heard at another.

*The x-ray features in the order of their significance are:*

1. *Differences* between inspiration and expiration progressively diminished.

2. *Contrast* increased between light and shadows

3. *Hyperillumination* over distended areas

4. *Sharpness* of structures not uniform; movement indicated in some areas while others are still.

5. *Diaphragm* more sloped and costophrenic sinus widened in upward and forward distending types.

*Diaphragm* flat and depressed, costophrenic sinuses obliterated in transverse and downward distending types

6. *Rib spacing increased* in distended parts

*Rib spacing decreased* in other parts

7. *Bronchogram* showing winter-tree picture.

Fluoroscopic signs of restriction in mobility of chest or diaphragm or both significantly aid the diagnosis. Increasing immobilization of chest is observed in all four forms above described. The diaphragm will long retain its mobility in the upward and forward distending forms (1 and 3) but eventually this too will become fixed. During the period of progressive mobilization of the diaphragm, its steplike movement, namely, reduced excursions at different levels varying as the patients try to breathe more deeply than usual, is very characteristic.

#### THE CLINICAL MANIFESTATIONS

The phasic evolution of the clinical course of pulmonary emphysema must be well appreciated if one is to understand this condition.

The three phases readily distinguished in the course of this long protracted disease are as follows:

1. Early compensated stage

2. Stage of inadequate compensation

3. Terminal decompensation stage.

1. The longest phase is that of well compensated emphysema which may be carried for many years, even decades, unrecognized by patient or even by physicians.

2. The second phase of inadequate compensation has also a considerably protracted course of some years (2 to 6). It manifests itself in two forms: a. Preponderant ventilatory insufficiency; b. Preponderant respirocirculatory insufficiency. In the former bronchospasm and bronchial infection play a conspicuous rôle. In the latter circulatory symptoms, namely venous engorgement and pulmonary congestion are added to the symptoms of emphysema.

3. The terminal decompensation phase is the shortest but its duration may also be variable, taking from a few weeks to many months or even a year. The duration depends largely upon whether decompensation takes the form of: a. predominant right heart failure or; b. combined left and right heart failure. In the former longer periods of recompensation may precede ultimate failure while in the latter the tendency is towards early syncopic end.

Other pertinent findings to be added from our observations are as follows:

Preponderant ventilatory insufficiency develops more frequently following primary pulmonary conditions while preponderant respirocirculatory insufficiency develops more frequently in emphysema complicating primary cardiac or cardiovascular conditions. However, we have observed the development of preponderant ventilatory insufficiency following primary cardiac conditions (arteriosclerotic heart disease) as well as the development of preponderant respirocirculatory insufficiency following primary pulmonary conditions (pulmonary fibrosis with Ayerza syndrome)

Predominant right heart failure is frequently the decompensation phase of pulmonary fibrosis and emphysema resulting from primary cardiovascular disease (mitral stenosis or hypertensive heart). It may be the terminal phase of primary pulmonary disease ending in heart failure.

Conversely, combined left and right heart failure is no more frequent as the end phase of primary cardiovascular conditions as it is of primary pulmonary conditions. Either of these conditions (cardiac or pulmonary) when present in chronic form may lead to chronic pulmonary fibrosis and emphysema.

The obvious conclusion from these observations is that the cardiopulmonary apparatus represents a single functional system. In this system it makes little difference whence the increased burden has arisen, it is shared by both equally and the effects will be identical for both. The ability of either the heart or the lungs to begin with, in carrying an increased functional burden (compensation) is the ultimate factor which determines the character of the insufficiency or failure syndrome. At times it is the heart which fails earlier in what began as a pulmonary condition, at other times it is the lungs which fail earlier in what began as a cardiac condition. Our observations have led us to the belief that in so-called left heart failure the ability of the lungs to adapt themselves rapidly to the suddenly increasing circulatory burden determines whether



the picture will be one of acute pulmonary edema or subacute cardiac asthma, or chronic cardiac emphysema.

The great difficulty in practice of differentiating between pulmonary and cardiac decompensation, in the vast majority of cases is a well recognized fact. It is often advocated that increase in the circulation time and venous pressure be accepted as the criteria for this distinction. The ingenious method of eliciting this increase (infusion test) in circulation time and venous pressure (artificially) showed that these criteria of functional failure may be produced also by purely pulmonary conditions.

The correlation between pulmonary and cardiac function is so close that the symptoms of decompensation and failure always represent the result of the disturbed function of both. Pathologically and clinically these are inseparable. The argument as to whether we are dealing with pulmonary or cardiac failure seems futile. We believe separate pulmonary or cardiac failure do not exist, there is only cardiopulmonary decompensation and failure.

#### TREATMENT

Our concluding remarks refer to a few points on treatment. Progression of emphysema may be slowed for a long time by controlling bronchopulmonary infections by chemotherapeutic treatment.

The treatment of ventilatory insufficiency consists of breathing exercises, inhalation of bronchodilator drugs and control of bronchopulmonary infections. Even primary cardiac conditions do not contraindicate the use of ephedrine if ventilatory insufficiency is present.

The treatment of respirocirculatory insufficiency consists of rest, vasodilator drugs (Aminophyllin or nitroglycerine) and  $O_2$  inhalation.

The treatment of right heart failure consists of digitalization combined with dehydration (mercuripurin).

The treatment of total heart failure consists of reduction of negative intrapulmonary pressure by positive pressure  $O_2$  inhalation, rapid decrease of venous return (phlebotomy) and control of excessive air hunger (producing excessive negative pressure in lungs) by moderate doses of morphine.

#### REFERENCES

1. CABOT, R. C., AND ADAMS, F. D.: Physical diagnosis, ed. 12, Baltimore, W. Wood & Co., 1938.
2. CHRISTIE, R. V.: Emphysema of the lungs. *Brit. M. J.*, pp. 105 and 143, 1944.
3. GORDON, I.: The mechanism of hypertrophic pulmonary emphysema. *Dis. of Chest*, 10:130, 1944.
4. MILLER, J. A., AND RAPPAPORT, I.: The relation of pulmonary function to fibrosis and emphysema. *Ann. Int. Med.*, 11:9, 1644, 1938.

## CEREBRAL ANEURYSM AS A CAUSE OF HEMIPLEGIA AND MASSIVE INTRACEREBRAL HEMORRHAGE<sup>1</sup>

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Spontaneous subarachnoid hemorrhage is probably the best known and most typical manifestation of "congenital" or berry aneurysm of the Circle of Willis and its branches. The problem of diagnosis is beset with many confusing elements in cases of aneurysm which simulate the picture of expanding brain tumor (1), encephalitis (2), meningo-radculitis (2), and chronic internal hydrocephalus (3). The casual student of the problem, like the writer, is unprepared for the statistical evidence of the high incidence of massive "apoplectic" brain hemorrhage in cases of aneurysm. In a series out of 27 cases reported in 1941 by Richardson and Hyland (1) 19 presented this complication. A year later Globus (4) reported 10 instances in a series of 20 verified cases. The former authors further computed an incidence of 22 per cent of massive intracerebral hemorrhages encountered in routine autopsies as being due to ruptured aneurysm of the Circle of Willis (1).

In a meticulous study of his cases Globus (4) demonstrated quite clearly that intracerebral rupture of such aneurysms occurred only under certain conditions, viz., when the contiguous brain substance had undergone previous softening by pressure necrosis so as to offer comparatively as little resistance to hemorrhagic infiltration as the subarachnoid space itself.

The background of this contribution by Globus is to be found in his earlier studies (5, 6) on the pathogenesis of massive apoplectic intracerebral hemorrhage and constitutes an extension and confirmation of the general thesis, first enunciated by Rouchoux (7) that apoplectic hemorrhage occurs in areas of previous brain softening. According to this theory, of which Globus is perhaps the most prominent modern exponent, hemorrhage results when the flow of arterial blood is maintained through exposed vessels in such areas of encephalomalacia, leading to rupture of the softened arterioles within tissue of greatly reduced "tensile strength." This presupposes an antecedent episode of interruption of arterial blood flow, either by thrombotic, atheromatous, or embolic occlusion, by buckling and kinking of dilated senile arteries ("serpentine aneurysm") within the internal carotid canal (Saphir (8)) or by direct mechanical compression. In cases of berry aneurysm pre-hemorrhagic softening of the brain may result from direct pressure by a large aneurysm upon the adjacent frontal or temporal lobe or from thrombotic occlusion of the parent arterial lumen by retrograde propagation of thrombus from the sac of the aneurysm. A third mechanism of brain softening which, to my knowledge, has not been previously reported existed in the case to be described below—mechanical compression of a cerebral artery by a small but very firm aneurysm.

<sup>1</sup> From the Percy Jones General and Convalescent Hospital, Battle Creek, Michigan.

## CASE REPORT

*History:* A private, aged 26 years, was admitted to Percy Jones General and Convalescent Hospital on January 8, 1944. While away on a pass before the New Year the patient drank a considerable quantity of liquor. On the following day he appeared at a nearby station hospital in a confused state, complaining of severe headache. Multiple bruises were seen over his forehead, cheekbones and upper lip. His pupils were equal, dilated and active. The deep reflexes were hyperactive. The admission diagnosis was acute alcoholism but blood analysis for alcohol was negative. His blood pressure was 110 systolic and 60 diastolic. The physical examination was otherwise negative.

*Course:* For five days the patient had constant headache and vomited frequently. On the sixth day he exhibited weakness of the entire right half of the body and impairment of speech. On transfer to the PJG&CHospital January 8, 1944 he displayed motor aphasia and complete right hemiplegia. His neck was rigid and retracted. His pupils were equal, regular and reacted to light. The fundi showed no papilledema. The Babinski sign was present on the right side and there was a right ankle clonus. A lumbar puncture revealed xanthochromic fluid under markedly increased pressure (400 mm. water plus). It was felt that the patient had had a spontaneous vascular accident with subarachnoid hemorrhage. Inasmuch as trauma could not be entirely excluded, he was explored for possible subdural hematoma.

*Operation and Postoperative Course:* Left subtemporal decompression revealed an extremely tense brain which was nonpulsating. Following the opening of the dura the brain began to pulsate and appeared soft. Needle exploration of the ventricles revealed slightly turbid fluid without evidence of hemorrhage.

On January 11, 1944 a ventriculography was attempted but the ventricle could not be entered. Two days later another lumbar puncture showed a drop in pressure to 120 mm. of water; the fluid was slightly yellow.

On January 25 the patient was able to move his right leg and in general appeared improved.

On February 6 he was able to walk around with help but still had considerable aphasia. Physiotherapy and reeducation were continued and preparations were made for his transfer to a veteran's hospital.

On the morning of February 26, approximately two months after the onset, the patient was found in a dazed condition sitting on the floor of his room. Repeated generalized convulsions occurred and these were poorly controlled with sodium pentothal. Acute pulmonary edema developed, succeeded by respiratory failure. The patient was kept breathing in a respirator and his left lateral ventricle was aspirated yielding grossly hemorrhagic fluid and blood clots. He died the following morning.

*Post mortem findings:* The subject was a moderately undernourished white male of 26 years, weighing about 150 pounds. There was moderate dependent lividity and moderate edema of the lower right forearm and hand. There were marked hyperemia and cyanosis of the forehead and scalp resulting from treatment in the resuscitator.

*Brain:* A well healed surgical scar was noted on the left side of the scalp above the ear overlying a large triangular subtemporal decompression defect in the skull, together with considerable edema and some hemorrhage of the deep scalp tissues about the defect. A corresponding defect was noted in the underlying dura exposing the surface of the brain which appeared softened and swollen, and which was partly extruded into the opening. Burr openings were present in the posterior portion of the skull on both sides with needle tracts through the underlying brain tissue. The cerebrospinal fluid had a purplish red tinge. The dura about the subtemporal opening exhibited brownish mottling from old hemorrhage.

A quantity of reddish black blood clot, more than an ounce in volume, welled out through the defect in the dura, apparently coming from a large irregular defect within the brain substance itself. The defect was then seen to represent a "blow-out" of softened hemorrhagic brain tissue exposing the cavity of the lateral ventricle beneath, from which consid-

erable fluid and clotted blood continued to drain through the opening. The brain substance about the defect showed a wide margin of softening which had a greyish brown discoloration. After removal of the calvaria diffuse recent subarachnoid hemorrhage was noted upon the entire surface of the brain. Small clots were present about the brain stem and upper cord and within the fourth ventricle. The left lateral ventricle was distended with blood clot and its lining tissue was discolored with old blood and yellowish necrosis, markedly pulpified, and compressed in several areas to less than 1 cm. in thickness. A small amount of blood clot and fluid blood was present also in the right lateral ventricle.

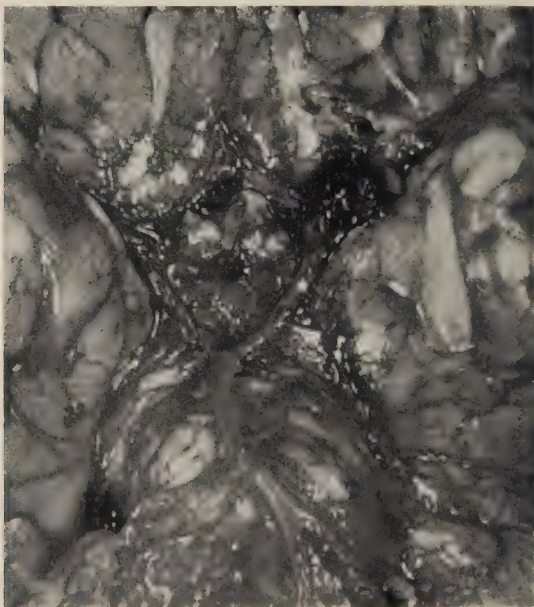


FIG. 1. Base of brain showing aneurysm of left internal carotid artery at the origin of the anterior and middle cerebral branches.

The Circle of Willis at the base of the brain appeared to be of normal arrangement. The basilar and both posterior communicating arteries were well formed and patent. A pea-sized smooth round aneurysm bulged out prominently from the angle at the bifurcation of the left internal carotid artery into the anterior and middle cerebral arteries. The aneurysm was unusually firm on palpation and did not exhibit any gross leaks. Injection of fluid into the basilar artery filled the entire Circle of Willis including both anterior cerebral and anterior communicating arteries. The left middle cerebral artery beyond the aneurysm did not fill. When the pia was stripped this artery was found completely collapsed and empty of blood. This change was found to begin at the site of the aneurysm which over-

lapped the inferior surface of the artery at its origin and exerted firm pressure upon it at this point. When opened, the left middle cerebral artery exhibited throughout a brownish yellow discoloration of its intima. No thrombi were found in any portion of its course. Section of the aneurysm revealed dark red organized thrombus filling its lumen but not extending into the lumen of its parent vessel.

*Lungs:* The posterior dependent portions of both lungs revealed congestion and some induration with loss of crepitation; on section these portions were dark purplish red in color and had a smooth fleshy cut surface. A moderate amount of mucopurulent exudate welled up into the bronchi from all lobes, especially the lower lobes.

*Heart:* It was firmly contracted and without significant abnormalities. The coronary vessels appeared normal.

*Liver:* On section the lobules appeared indistinct and the central areas appeared relatively bloodless and somewhat greyish in color.

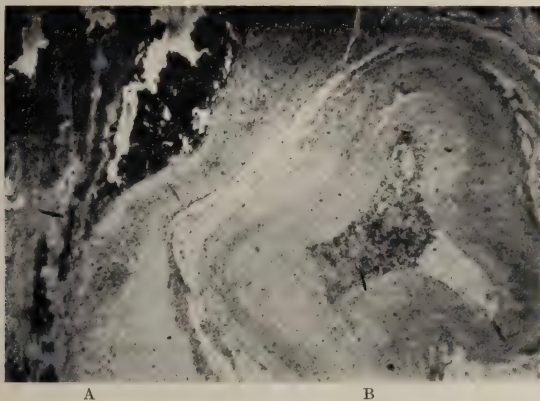


FIG. 2. Photomicrograph showing sac of aneurysm (A) in contact with middle cerebral artery, (B) showing compression with narrowing of lumen.

*Spleen:* It displayed slight enlargement; it weighed 180 grams, and was rather fleshy, exhibiting a smooth glassy cut surface, slightly translucent, of light brownish red color with greyish overcast.

*Kidneys:* Both kidneys were moderately congested. No cysts were observed. The urinary bladder was markedly distended with light colored urine.

*Gastro-intestinal Tract:* The stomach was moderately contracted but free of erosions and hemorrhage. The duodenum and small intestine were contracted. The large intestine was markedly contracted and contained a small amount of formed feces and some whitish mucus. Petechial hemorrhages were noted in the mucosa of the terminal ileum and rectum.

#### *Microscopic observations:*

*Aneurysm:* The wall of the aneurysm was composed of hyalinized connective tissue continuous externally with the adventitia of the nearby artery. Scattered leukocytes and macrophages containing blood pigment were seen in the adventitial tissues. At one point the sac wall exhibited beginning eosinophilic necrosis with considerable hemorrhagic infiltration within its layers but no actual disruption in the sections studied.



The lumen of the aneurysm was almost entirely filled with laminated thrombus heavily impregnated with blood cells, and showing considerable organization by plump stellate fibroblasts and mild infiltration of leukocytes, chiefly eosinophiles and lymphocytes. A small residual lumen was present near its center lined with a layer of compact fibrin with superimposed deposit of thrombus. Vestiges of arterial media and elastica interna could be traced from the parent artery into the neck of the aneurysmal sac for a short distance and were then lost in the fibrous tissue forming the sac wall.

The collapsed middle cerebral artery exhibited a segment of moderate thickening by loose fibrous intimal hyperplasia of reactive type. The intimal thickening was exaggerated by the contraction of the artery, both factors resulting in considerable reduction in size of its lumen which was empty. The wall of the artery was markedly indented and its lumen narrowed by the directly contiguous sac of the adjacent aneurysm reducing its lumen at one point to an irregular branching cleft.

*Brain:* Sections through softened areas of the cortex revealed massive disorganization of grey and white matter with extensive rarefaction and marked loss of cells. The line of separation between grey and white matter was difficult or impossible to define. Many compound granular corpuscles containing granular material were present in the remnants of grey matter which also exhibited marked spongy rarefaction of the glial matrix and a few gemistocytic astrocytes. Nerve cells appeared to be totally destroyed. Within the remnants of white matter the fibre tracts appeared markedly shredded and disorganized and appeared to have lost all continuity. Numerous large eosinophilic myelophages were present. In one section an area of recent hemorrhage was seen. There was considerable edema and degeneration of ganglion cells in the marginal tissue about the necrotic areas. Many blood cells were present in the overlying subarachnoid space.

Sections through the brain stem in the region of pons and medulla revealed a few fairly large foci of hemorrhage with surrounding tissue necrosis. The hemorrhages were streak shaped and apparently perivascular. Patchy spongy rarefaction was seen in the descending myelinated fibres in the pons corresponding to the left pyramidal tract.

*Lung:* The pulmonary tissue had the appearance of prolonged atelectasis; bronchioles and alveoli exhibited epithelial proliferation and their lumens were markedly compressed and partly filled with large numbers of alveolar phagocytes containing brownish granular pigment. There was moderate capillary congestion and mild edema. Leukocytic exudate was present within some of the bronchioles and their tributary alveoli.

*Spleen:* Mild uniform reticulum cell hyperplasia and thickening of reticulum framework were noted. The sinusoids were contracted and relatively bloodless.

*Liver:* The sinusoids were narrow and contained little blood.

*Prostate:* Many corpora amylacea were present. There was moderate submucous infiltration of lymphocytes within the prostatic urethra.

*Pituitary:* There was slight reduction in glandular elements of the pars anterior and some fibrous thickening of the stroma.

#### COMMENT

The clinical and anatomical data in this case lend themselves readily to clinico-pathologic correlation. Three principal episodes were defined, 1. the initial subarachnoid hemorrhage, 2. the phase of hemiplegia, and 3. the terminal massive intracerebral hemorrhage. These can all be related to pathologic events occurring within and about the aneurysm. The primary incident must be presumed to have been the development of a mild leak in the sac of the aneurysm, possibly the result of overstretching provoked by hydremic plethora from the excessive intake of alcoholic beverages in celebration of the New Year. Healing of the leak was apparently accomplished by thrombosis of the aneurysm with

subsequent organization and no leak was evident when the subject came to autopsy. The occurrence of hemiplegia and aphasia on the sixth day appears to have been the direct result of the formation of this thrombus, which, as demonstrated post mortem, had caused hardening of the aneurysm of such degree that the mechanical compression it exerted upon the adjacent middle cerebral artery was sufficient to occlude it nearly completely and produce encephalomalacia. Within the ensuing seven weeks a considerable measure of clinical improvement was seen in the patient, both in the paralysis and in the aphasia. It is not improbable that the occlusion was of partially remittent type so that an intermittent slight flow of blood occurred, aiding in the recovery of function. Nevertheless an extensive area of necrosis was still evident at autopsy and showed histological evidences of long duration compatible with that of the hemiplegia itself (seven weeks). The terminating event was massive intracerebral hemorrhage within the area of softening and of such extent that rupture occurred into the ventricles and subarachnoid space and death followed in less than 24 hours.

From the point of view of the Rouchoux-Globus postulate of "pre-hemorrhagic brain softening" in apoplectic hemorrhage this case constitutes a particularly appropriate example and earns thereby its chief warranty for publication. In his recent series of 10 cases of cerebral aneurysm with massive intracerebral hemorrhage Globus and Globus demonstrated softening of brain tissue in the neighborhood of the aneurysm resulting primarily from the direct pressure of the latter. The existence of softening antecedent to massive hemorrhage was amply established by the gross and microscopic changes in the tissue; however clinical signs or symptoms of pre-hemorrhagic softening were lacking in these cases because of the localization of the majority of these aneurysms in the rostral portion of the Circle of Willis contiguous to "silent areas" of the brain. The present case may be considered unique, therefore, in providing data on both clinical localization and duration of the pre-hemorrhagic softening. Its further interest lies in the peculiar accident of relation between the aneurysm and the middle cerebral artery in which obstruction was encompassed in the latter by direct mechanical compression by the aneurysm following its thrombosis.

Brief mention may be made at this time of an incidental finding in the spleen of this case which the writer has seen also in other cases of intense cerebral irritation caused by spontaneous or post-traumatic subarachnoid bleeding. Grossly the spleen appeared shrunken and blanched; microscopically the sinusoids were markedly narrowed and almost completely bloodless. This change, which parallels the effect of epinephrine upon the spleen, is believed to reflect a state of intense sympathicotonia existing *ante mortem*, probably associated with hyperepinephrinemia. It may be further correlated with hyperglycemia, hypertension, pulmonary edema, and albuminuria which are commonly noted clinically in subarachnoid hemorrhage and ascribable to the same mechanisms.

#### SUMMARY

A case of berry aneurysm of the Circle of Willis arising from the left internal carotid artery at the origin of the middle cerebral artery is reported. Death

was caused by massive apoplectic hemorrhage with rupture into the ventricles. At necropsy the aneurysm was found to have occluded the left middle cerebral artery by direct mechanical compression resulting in encephalomalacia which was signalized clinically by left hemiplegia and aphasia occurring seven weeks previously. The data in this case provide further confirmation of the correctness of the Rouchoux-Globus theory of pre-hemorrhagic brain softening as an antecedent factor in massive apoplectic intracerebral hemorrhage.

## REFERENCES

1. RICHARDSON, J. C., AND HYLAND, H. H.: Intracranial Aneurysms; A Clinical and Pathological Study of Subarachnoid and Intracerebral Haemorrhage Caused by Berry Aneurysms, *Medicine*, 20: 1, 1941.
2. GLOBUS, J. H., AND SCHWAB, J. M.: Intracranial Aneurysms; Their Origin and Clinical Behavior in a Series of Verified Cases, *J. Mt. Sinai Hosp.*, 8: 547, 1942.
3. STRAUSS, I., GLOBUS, J. H., AND GINSBURG, S. W.: Spontaneous Subarachnoid Hemorrhage, *Arch. Neurol. & Psychiat.*, 27: 1080, 1932.
4. GLOBUS, J. H., assisted by GLOBUS, RUDO S.: Cerebral Aneurysm and Massive Non-Traumatic Cerebral Hemorrhage, *J. Neuropath. & Exper. Neurol.*, 2: 365, 1943.
5. GLOBUS, J. H., AND STRAUSS, I.: Massive Cerebral Hemorrhage; Its Relation to Pre-existing Cerebral Softening, *Arch. Neurol. & Psychiat.*, 28: 215, 1927.
6. GLOBUS, J. H.: Massive Cerebral Hemorrhage, *Proc. A. Res. Nerv. & Ment. Dis.*, 18: 438, 1937, *J. Mt. Sinai Hosp.*, 5: 657, 1939.
7. ROUCHOUX: cited by Globus (4).
8. SAPHIR, O.: Serpentine Aneurysm of the Internal Carotid Artery with Resulting Encephalomalacia and Cerebral Hemorrhage, *Arch. Path.*, 20: 36, 1935.

# PLASMA VITAMIN A AND CAROTENE IN DIABETES MELLITUS<sup>1</sup>

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Plasma vitamin A and carotene determinations in 11 normal persons and 114 diabetics were recently published (1). During last winter 24 additional normals and 32 diabetics were examined. With more data available, especially for the normal group, it was thought worth while to check the previous conclusions which were not entirely in accord with the accepted findings for plasma vitamin A and carotene in diabetes mellitus.

## CLINICAL MATERIAL

One hundred and twelve juvenile diabetic subjects from 6 to 18 years of age were observed at Camp Nyda, a children's summer camp conducted by the New York Diabetes Association, Inc. Most of them came from the diabetes clinics in Greater New York, though a few were private patients referred by their physicians. In addition 34 adult diabetics of varying ages, living in New York City, were studied. This makes a total of 146 cases of diabetes included in the present report. The control group of 35 normals consisted of adults, physicians, laboratory workers, and their friends and relatives.

## METHODS

The determinations were all made while the subjects were fasting, that is before breakfast. The methods employed were those previously described (1).

## NORMAL VALUES

The plasma carotene content ranged from 34 to 272 micrograms per 100 cc. There were a sufficient number of instances below 100 (8 individuals) and above 200 (7 individuals) (see Chart 1) to make it certain that these wide variations in normal values were correct.

The plasma vitamin A level in the normal series varied from 27 to 81 micrograms per 100 cc.

## DETERMINATION IN DIABETICS

The complete results obtained in normals and diabetics are given in Chart 1 and summarized in Table 1. In recording the values in Chart 1 and Table 1, each figure represents a separate individual. When more than one observation was made on the same person, only the mean of such determinations was put down.

*Carotene:* About fifteen years ago Boeck and Yater (2), as well as Rabinowitch (3) demonstrated an excess of carotene in the blood in more than 85 per cent of diabetics. Subsequent publications verified these findings until Gordon and

<sup>1</sup> From the Research Division of the New York Diabetes Association, Inc. Aided in part by a grant from Mr. Felix Morgenstern.

Sevringhaus (4) failed to duplicate them. In the present series 76 per cent of the diabetics yielded plasma carotene values within the normal range and 24 per

### PLASMA CAROTENE AND VITAMIN A VALUES IN 35 NORMALS AND 146 DIABETICS

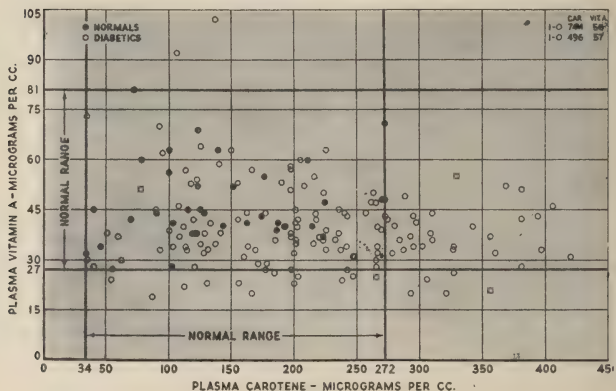


CHART 1

Most diabetics are within normal range (Vitamin A 87 per cent, carotene 76 per cent) though there is a tendency in the diabetics for the Vitamin A to be subnormal (11.6 per cent) and the Carotene to be above normal (24 per cent). Studies of diabetics 15 years ago revealed an excess of Plasma Carotene in 85 per cent (Boeck and Yater, Rabinowitch).

TABLE 1

*Summary of results, plasma carotene and vitamin A determinations in 35 normal persons and 146 cases of diabetes.*

| PLASMA CAROTENE MICROGRAMS PER 100 CC.  |   |
|---|---|
| Normal.....                             | range, 34 to 272                          |
| Diabetic.....                           | range, 35 to 744                          |
| Diabetics.....                          | 35 cases, 24.0 per cent above normal      |
| Diabetics.....                          | 0 cases, 0.0 per cent below normal        |
| Diabetics.....                          | 111 cases, 76.0 per cent in normal range. |
| PLASMA VITAMIN A MICROGRAMS PER 100 CC. |   |
| Normal.....                             | range, 27 to 81                           |
| Diabetic.....                           | range, 19 to 102                          |
| Diabetics.....                          | 2 cases, 1.4 per cent above normal        |
| Diabetics.....                          | 17 cases, 11.6 per cent below normal      |
| Diabetics.....                          | 127 cases, 87.0 per cent in normal range. |

cent above the normal. It is evident that the hypercarotenemia prevalent in diabetics more than a decade ago has largely disappeared under present day



treatment, so that in most cases the plasma carotene is within normal limits and above normal in only a few.

*Vitamin A:* Finding 87 per cent of the diabetics within normal limits and 2 cases showing higher than normal values reverses the accepted opinions and also

TABLE 2

*Plasma carotene and vitamin A in diabetes when two or more determinations were made in the same subject. The constant values in each case indicate a persistent pattern characteristic of the individual's metabolism, in which the diabetes may play a rôle, but evidently is not the controlling factor.*

(In recording the values in chart 1 and table 1 only the mean of the determinations in individual is used.)

| DATE           | PLASMA<br>CAROTENE                | PLASMA<br>VITAMIN A               | DIAGNOSIS AND REMARKS   |
|----------------|-----------------------------------|-----------------------------------|---|
|                | <i>Micrograms<br/>per 100 cc.</i> | <i>Micrograms<br/>per 100 cc.</i> |   |
| Jan. 24... ..  | 624                               |                                   | Male, age 49, mild diabetes, good control, hyperlipemia (carotene persistently high.)                                     |
| Feb. 21... ..  | 750                               | 46                                |   |
| March 6... ..  | 763                               | 65                                |   |
| March 20... .. | 839                               |                                   |   |
| Dec. 20... ..  | 91                                | 59                                | Male, age 42, diabetes exceedingly poor control, hyperlipemia.  |
| Jan. 17... ..  | 162                               |                                   |   |
| Feb. 14... ..  | 166                               |                                   |   |
| Dec. 20... ..  | 129                               | 96                                | Male, age 39, diabetes good control, advanced degree of nephritis. (Vitamin A persistently high.)                         |
| Jzn. 17... ..  | 130                               | 102                               |   |
| Feb. 14... ..  | 152                               | 107                               |   |
| Feb. 10... ..  | 98                                | 27                                | Male, age 22, diabetes.   |
| Feb. 17... ..  | 151                               | 42                                |   |
| Jan. 22... ..  | 125                               | 66                                | Male, age 54, diabetes.   |
| Feb. 12... ..  | 124                               | 62                                |   |
| Feb. 14... ..  | 106                               | 45                                | Male, age 54, diabetes.   |
| Feb. 24... ..  | 115                               | 35                                |   |
| Jan. 3... ..   | 51                                |                                   | Male, age 45, diabetes under good control, hyperlipemia regarded as idiopathic hyperlipemia, independent of the diabetes. |
| Jan. 31... ..  | 45                                | 39                                |   |
| Feb. 28... ..  | 53                                | 38                                |   |
| March 13... .. | 56                                | 38                                |   |
| Dec. 29... ..  | 38                                | 56                                | Male, age 54, diabetes under good control, Gaucher's disease.   |
| Jan. 26... ..  | 39                                | 49                                |   |
| March 6... ..  | 33                                | 45                                |   |

our previous conclusions regarding the prevalence of low levels of plasma vitamin A in diabetes. However, it is both logical and plausible that when carotene which is considered to be a precursor of vitamin A conforms to the usual pattern, vitamin A should do the same.

## DISCUSSION

The hypercarotenemia and the depression of plasma vitamin A which were the rule in diabetes more than a decade ago, are now the exception. The reason for this, apparently, lies in the more effectual management of the disease. Exactly what factors have been involved is not clear. It has been suggested that impairment of liver function (5) may have been responsible, for the liver is concerned with the change of carotene to vitamin A and the storage of vitamin A. It may have been due to a derangement of the fat metabolism (6), since the absorption, transport and possibly storage of the fat soluble carotene and vitamin A depend upon fat. Perhaps both were contributing factors. No final conclusion on this subject has been formulated.

One point is noteworthy: The plasma carotene and vitamin A levels follow distinct patterns in each diabetic (Table 2). Thus it would appear that every case of diabetes has metabolic processes influencing carotene and vitamin A, in which the diabetes may play a role, but it is not necessarily the controlling factor.

## CONCLUSIONS

The majority of diabetics to-day, in contrast to a decade or more ago, have plasma carotene and vitamin A levels that are within normal limits. There is a tendency for the carotene to be elevated (24 per cent of the cases) and the vitamin A to be depressed (11.6 per cent of the cases). Factors, as yet undetermined other than the diabetes itself, are the dominating influences which regulate the plasma carotene and vitamin A, so that each case of diabetes maintains the characteristic values of carotene and vitamin A in the blood that may distinguish it from other diabetics.

## REFERENCES

1. MOSENTHAL, H. O., AND LOUGHLIN, W. C.: Vitamins A, B and C in diabetic children. *Arch. Int. Med.*, 73: 391, 1944.
2. BOECK, W. C., AND YATER, W. M.: Xanthemia and xanthosis (carotinemia): Clinical study. *J. Lab. & Clin. Med.*, 14: 1129, 1929.
3. RABINOWITCH, I. M.: Carotinemia and diabetes: Relationship between sugar, cholesterol and carotene contents of blood plasma. *Arch. Int. Med.*, 45: 586, 1930.
4. GORDON, E. S., AND SEVRINGHAUS, E. L.: *Vitamin Therapy and General Practice*, ed. 2, Chicago, Year Book Publishers, Inc., 1942.
5. RALLI, E. P., PARIENTE, A. C., BRANDALEONE, H., AND DAVIDSON, S.: Effect of carotene and vitamin A on patients with diabetes mellitus: Effect of daily administration of carotene on blood carotene of normal and diabetic individuals. *J. A. M. A.*, 106, 1975, 1936.
6. MURRILL, W. A., HORTON, P. B., LEIBERMAN, E., AND NEWBURGH, L. H.: Vitamin A and carotene: Vitamin A and carotene metabolism in diabetics and normals. *J. Clin. Investigation*, 20: 395, 1941.

## MASSIVE PULMONARY EMBOLISM VI<sup>1</sup>

BASED IN PART ON A STUDY OF EIGHTY-EIGHT FATAL CASES<sup>2</sup>

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### IV. THE PROBLEM OF DIAGNOSIS OF PULMONARY EMBOLISM

Due to the fact that pulmonary embolism and coronary artery thrombosis may produce similar and, at times, identical clinical manifestations, the differential diagnosis between these two conditions is often difficult and may even be impossible [Hamman (81), Pilcher (78), Hazard & Salmon (82), Gorham (83), Barnes (1), McGinn & White (79), Averbuck (84), Hamburger and Saphir (85), Nygaard (86), Petterson (127)].

Horn, Dack and Friedberg (80) suggest that the striking similarity of the clinical picture in pulmonary embolism and acute coronary thrombosis may actually result from a diminution of the coronary circulation and associated ischemia of the myocardium. These workers studied a group of 42 cases of pulmonary embolism, in 8 of which recent structural changes in the myocardium ordinarily resulting from acute myocardial ischemia were revealed. They state that the factors necessary for the production of the myocardial ischemia in these cases are shock, asphyxia and exaggerated vagal reflexes resulting from the embolic obstruction of the pulmonary arteries. These factors, alone or in association, lead to insufficiency of the coronary circulation. Thus the resemblance of electrocardiographic changes in cases of embolism of the pulmonary artery to those in cases of myocardial infarction of the posterior wall can be explained by the diminished flow through the right coronary artery resulting from increased tension in the right ventricle. The authors also state that morphologic evidence of coronary insufficiency in cases of embolism of the pulmonary artery is more likely to exist if there are recurrent embolizations, narrowing of the coronary arteries, cardiac hypertrophy, and sufficient duration of life after embolism.

On the other hand, Love, Brugler and Winslow (87) state that shock may induce electrocardiographic curves similar to those of coronary artery occlusion if the coronary arteries are already narrowed, but that these curves are not similar to those obtained in pulmonary embolism.

Acute pulmonary embolism and acute coronary thrombosis may have the following in common (Barnes 1, 88): Sudden onset; pallor and sweating; pre-

<sup>1</sup> This is the sixth installment of a series of articles dealing with the problem of Massive Pulmonary Embolism. Upon completion of their publication they will be collected and reprinted in a single volume, constituting one of the Series of projected Monographs of The Mount Sinai Hospital Press.—Ed.

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<sup>3</sup> Major Klein, adjunct surgeon to The Mount Sinai Hospital and now serving overseas with the Mount Sinai Hospital Unit, has contributed the study of the fatal cases and the analysis on which the work is based.

cordial pain; weakness; vomiting; collapse; marked fall in blood pressure and acceleration of the pulse; leukocytosis; elevation in temperature. He states, however, that cyanosis and extreme dyspnea are encountered much more frequently in acute pulmonary embolism than in acute coronary thrombosis. Pain, on the other hand, is more severe and prolonged with acute coronary occlusion and is usually referred to the sternal region, while the pain of pulmonary embolism is usually referred to the lateral regions of the thorax and may be made worse by inspiration. According to Barnes, physical examination in the early stages is not particularly helpful in the differential diagnosis. A previous history of angina pectoris should incline one to favor the diagnosis of coronary occlusion.

McGinn and White (79) noted that the majority of the clinical symptoms of pulmonary embolism as observed in their nine cases of massive pulmonary embolism with acute cor pulmonale are also commonly found in coronary thrombosis. They include chest pain or substernal oppression; elevation in the temperature, in the pulse and respiratory rates, and the white cell count; collapse; sweating and pallor; and a fall in blood pressure.

Most difficult of diagnosis are those cases of pulmonary embolism in which there is concomitant coronary artery disease [Hamburger and Saphir (85)]. Averbuck (84) reported six cases in which fatal attacks of coronary artery thrombosis were diagnosed but in which necropsy revealed pulmonary embolization to have been the cause of death. In two instances the diagnosis was made particularly difficult by the fact that coronary artery disease had previously been present and its existence was confirmed by the history, physical and laboratory findings. Nevertheless, the fatal episode was caused by pulmonary embolization. Averbuck emphasizes the necessity for great caution in the diagnosis of coronary artery thrombosis in patients presenting the syndrome under consideration in the absence of a previous history suggestive of coronary artery disease. Levine and Brown (89) were able to obtain such information in the majority of cases which they studied and lay great stress on its diagnostic value. Averbuck makes another point namely, that pulmonary embolization is frequent after operation and that coronary artery thrombosis is comparatively rare because patients with coronary disease are rarely subjected to any but emergency surgical procedures.

Analysis of cases observed at The Mount Sinai Hospital over a six-year period reveals the same incidence of postoperative coronary thrombosis and fatal pulmonary embolism. In a series of 625 attacks of coronary artery occlusion, verified by electrocardiogram or autopsy, which were treated in The Mount Sinai Hospital during the years 1931 to 1937, Master, Dack and Jaffee (126) noted that 35 occurred following operation. Forty-six of our 88 cases of fatal pulmonary embolism, verified by necropsy, occurred in this hospital during the same period. Eleven of these were in medical cases. Thirty-five occurred in surgical patients during the postoperative period. Master, Jaffee and Dack (90) indicate a diagnostic point which they believe to be important in the differentiation between coronary thrombosis and pulmonary embolism, namely, that the dyspnea of coronary thrombosis is relieved by oxygen therapy while the dyspnea of

pulmonary embolism is uncontrollable and unrelieved by treatment with oxygen.

It is claimed by various authors that pulmonary embolism produces characteristic alterations in the electrocardiogram which may be of aid in the diagnosis. Based on a study of their cases of acute cor pulmonale caused by massive embolic obstruction of the pulmonary arterial circulation, White (62) and McGinn and White (79) have described the following electrocardiographic findings: An upright T-wave with relatively normal P and QRS waves, with return to normally inverted T-waves when the acute cor pulmonale subsided. This picture differs from lead IV of coronary thrombosis of either the T1 or T3 types.

Barnes (1, 88) corroborates the electrocardiographic findings of White (62), and McGinn and White (79) in acute pulmonary embolism, and observes that the electrocardiographic tracing obtained in acute myocardial infarction involving the posterior basal portion of the left ventricle resembles very closely that following acute pulmonary embolism. There are, however, certain distinguishing differences in the electrocardiograms of the two conditions, which are outlined as follows:

| <i>Type of Electrocardiogram Characteristic of Acute Pulmonary Embolism</i>    | <i>T<sub>3</sub> Type of Electrocardiogram, Characteristic of Acute Infarction of the Posterior Portion of the Left Ventricle</i> |
|--|---|
| S <sub>1</sub> constantly present and usually prominent                        | S <sub>1</sub> absent or, if present, not exaggerated   |
| S-T <sub>2</sub> —Take off usually below zero level                            | R-T <sub>2</sub> usually elevated; rarely isoelectric and never depressed   |
| T <sub>2</sub> diphasic, monophasic, or upright; rarely inverted               | T <sub>2</sub> usually inverted   |
| R-T <sub>3</sub> occasionally slightly elevated                                | R-T <sub>3</sub> much elevated as a rule  |
| T <sub>3</sub> inverted; may be cove plane                                     | T <sub>3</sub> usually inverted   |
| Q <sub>3</sub> frequently fairly prominent; Q <sub>3</sub> pattern not present | Q <sub>3</sub> frequently markedly prominent; Q <sub>3</sub> pattern commonly present   |
| Q <sub>4</sub> usually within normal limits                                    | Q <sub>4</sub> usually within normal limits   |
| T <sub>4</sub> usually upright; may be flat or diphasic                        | T <sub>4</sub> usually inverted   |

Electrocardiograms following pulmonary embolism or infarction, as observed by Love and his co-workers (87) have also shown depression of the ST segments in one or more leads, most frequently in lead II, and often the reversal of the direction of the T-waves in lead III and the precordial lead.

In an extensive study of the subject, Katz (91) states that the classical electrocardiographic change in pulmonary embolism tends to resemble the posterior wall type in the limb leads and the anterior in the chest leads. However, the S-T deviation is confined to leads, I, II and CF<sub>4</sub>, consisting of a depression with "staircase" ascent, that is, an upward slope to the S-T segment. There is a tendency for an S type of QRS to appear in lead I along with a Q type in lead III. The QRS contour in the chest leads, however, remains unchanged. Characteristically, the T-wave is inverted in leads III and CF<sub>2</sub> but not usually in leads II and CF<sub>4</sub>. When seen, this pattern is almost pathognomonic, but the entire



picture occurs in only about 10 per cent, of the cases. One or more of the individual changes described above are seen more frequently than the entire combination. The temporary appearance of a right axis shift, sometimes resembling right preponderance, should be considered a suggestive finding. Katz states that in a large percentage of cases of pulmonary embolism, however, non-specific changes of no diagnostic significance occur. The diagnosis of pulmonary embolism must rest on an awareness of its possibility, and the suspicion of its presence when atypical electrocardiographic features which superficially resemble coronary contour are noted following an acute episode. The evolution in these cases aids in their differentiation from myocardial infarctions. The magnitudes of the S-T deviation and the T-wave size seen in myocardial infarctions are absent, and the time course is more rapid in pulmonary embolism.

In the experience of Master and his associates (90), however, the characteristic progressive changes in the electrocardiogram, that is R-T segment and T-wave changes, are found only in coronary thrombosis. They state that in coronary thrombosis, characteristic *progressive* daily changes occur, consisting of elevation of the R-T segment to inversion of the T-wave. It is their opinion that the electrocardiographic criteria for pulmonary embolism of McGinn and White have been only suggestive and the simulation of the electrocardiogram of coronary thrombosis is close enough to make the diagnosis uncertain.

Other conditions with which pulmonary embolism may be confused are shock and hemorrhage, peritonitis, pulmonary edema, coma, and cerebral vascular accidents [Nygaard (86)]. Ware and Bullock (92) include spontaneous pneumothorax, dissecting aortic aneurysm, pneumonia, pulmonary atelectasis, acute upper abdominal accidents and perforating peptic ulcer. Petterson (127) considers acute heart failure to be the most difficult condition to differentiate from lung embolism.

In a study of 43 fatal cases in which necropsy showed pulmonary embolism to have been the immediate cause of death, Johnson (94) found that only three cases answered the description of pulmonary embolism. In nine cases the clinical picture was so atypical that the diagnosis of pulmonary embolism was unwarranted, even in retrospect. Furthermore, there were a significant number of patients who presented a sufficient number of clinical criteria to warrant a diagnosis of pulmonary embolism but in whom the pathologist found sepsis, without evidence of embolism, as the cause of death. According to this author, there appears to be no single feature short of necropsy by which the diagnosis of pulmonary embolism can be infallibly established or excluded.

On the basis of his experience and the experience of others, both in living patients and at autopsy, Wright (97) states that in all probability more than half of all pulmonary emboli are missed entirely or are wrongly diagnosed.

In our series of 88 cases, the correct diagnosis of pulmonary embolism was made unequivocally in only 16 (Table 8).<sup>4</sup> In 13 other instances, pulmonary embolism was considered, but alternative diagnoses were also made (Tables 8

<sup>4</sup> Table 8 appeared in the article, "Massive Pulmonary Embolism, III," published in this Journal, vol. 11, p. 241, 1944.

and 10). These included coronary thrombosis, paroxysmal tachycardia, cardiac failure, insulin shock, perforated gastric carcinoma and cerebral lesions. Thus, pulmonary embolism was diagnosed either definitely or equivocally in a total of 29 patients. The diagnosis was incorrect in 22 cases (Tables 8 and 11). Finally, there were 37 cases in which there were no notes on the charts to indicate the clinical impression of the cause of death. After carefully reviewing the clinical features, we believe that the diagnosis of pulmonary embolism could or should have been made in 24 of these 37 cases. We have no means of ascertain-

TABLE 10

*Alternative Diagnoses Entertained with that of Pulmonary Embolism*

|  |          |
|--|----------|
| Pulmonary embolism or coronary thrombosis.....                           | 5 cases  |
| Multiple pulmonary emboli or coronary thrombosis.....                    | 1        |
| Pulmonary embolism or coronary thrombosis or paroxysmal tachycardia..... | 1        |
| Pulmonary embolism or cardiac failure.....                               | 1        |
| Pulmonary embolism or insulin shock.....                                 | 1        |
| Pulmonary embolism or cerebral embolism.....                             | 1        |
| Pulmonary embolism or cerebral accident.....                             | 1        |
| Pulmonary embolism or perforation of gastric carcinoma.....              | 1        |
| Pulmonary infarct or coronary thrombosis or heart failure.....           | 1        |
| Total.....   | 13 cases |

TABLE 11

*Incorrect Diagnoses of Fatal Pulmonary Embolism*

|   |          |
|---|----------|
| Coronary thrombosis.....                                | 7 cases  |
| Coronary thrombosis or subarachnoid bleeding.....       | 1        |
| Coronary thrombosis or hemorrhage into brain tumor..... | 1        |
| Cardiac or cerebral death.....                          | 1        |
| Cardiac collapse or cerebral hemorrhage.....            | 1        |
| Cardiac failure.....                                    | 3        |
| Functional myocardial involvement.....                  | 1        |
| Circulatory collapse.....                               | 1        |
| Cerebral thrombosis.....                                | 1        |
| Cardiac failure or peritonitis.....                     | 1        |
| Peritonitis or pneumonia.....                           | 1        |
| Bronchopneumonia.....                                   | 2        |
| Carcinomatous cachexia.....                             | 1        |
| Total.....  | 22 cases |

ing in what proportion of these cases the diagnosis was entertained. It can be stated definitely, however, that in 13 cases, the clinical picture did not warrant the diagnosis of pulmonary embolism (Table 8).

BIBLIOGRAPHY<sup>6</sup>

94. JOHNSON, A. S.: Antemortem Recognition of Pulmonary Embolism, New England J. Med., 222: 793, 1940.

<sup>6</sup> Preceding references appeared appended in previous chapters.

95. GRAY, H. K.: The Use of the Trendelenburg Position in the Prevention of Post-operative Pulmonary Complications, *Proc. Staff Meet., Mayo Clinic*, 9: 453, 1934.
96. POTTS, W. J.: Pulmonary Embolism, *Ann. Surg.*, 111: 554, 1940.
97. WRIGHT, I. S.: Thrombophlebitis, *Bull. New York Acad. Med.*, Second Series, 17: 348, 1941.
98. WALTERS, W.: A Method of Reducing the Incidence of Fatal Postoperative Pulmonary Embolism: Results of its Use in 4,500 Surgical Cases, *Surg., Gynec. & Obst.*, 50: 154, 1930.
99. MURRAY, D. W. G.: Some Experimental and Clinical Aspects of the Use of Heparin. *Surg., Gynec. & Obst.*, 70: 246, 1940.
100. MURRAY, D. W. G., AND BEST, C. H.: The Use of Heparin in Thrombosis, *Ann. of Surg.*, 108: 163, 1938.
101. LAM, C. R.: Heparin Administration: Method and Results in Thirty Cases, *Ann. Surg.*, 114: 205, 1941.
102. MURRAY, D. W. G.: Heparin in Thrombosis and Blood Vessel Surgery, *Surg., Gynec. & Obst.*, 72: 340, 1941.
103. CRAWFORD, C., AND JOOPES, E.: Heparin as a Prophylactic Against Thrombosis, *J. A. M. A.*, 116: 2831, June 28, 1941.
104. PRIESTLEY, J. T., ESSEX, H. E., AND BARKER, N. W.: The Use of Heparin in the Prevention and Treatment of Postoperative Thrombosis and Embolism, *Proc. Staff Meet., Mayo Clinic*, 16: 60, 1941.
105. LINK et al., cited by Meyer, O. O., et al., ref. 107.
106. MEYER, O. O., BINGHAM, J. B., AND POHLE, J. J.: The Effect of the Synthetic Dicoumarin 3,3'-Methylenebis (4-Hydroxycoumarin) on the Prothrombin Time and Coagulation Time, *J. A. M. A.*, 118: 1003, 1942.
107. QUICK, A. J.: Discussion of paper of Meyer, O. O., Bingham, J. B., and Pohle, F. J., *J. A. M. A.*, 118: 1004, 1942.
108. BARKER, N. W.: Discussion of paper of Meyer, O. O., Bingham, J. B., and Pohle, F. J., *J. A. M. A.*, 118: 1004, 1942.
109. EVANS, J. A.: The Combined Use of Heparin and Dicoumarin (3,3' Methylenebis, 4-Hydroxycoumarin) in Thrombophlebitis and Pulmonary Embolism (Preliminary Report), *Lahey Clinic Bull.*, 2: 248, 1942.
110. HOMANS, J.: Exploration and Division of the Femoral and Iliac Veins in the Treatment of Thrombophlebitis of the Leg, *New England J. Med.*, 224: 179, 1941.
111. VEAL, J. R.: High Ligation of the Femoral Vein in Amputations of the Lower Extremities, *J. A. M. A.*, 114: 1616, 1940.
112. SEARS, J. B.: Experience with Femoral-Vein Ligation for Prophylaxis of Post-operative Pulmonary Embolism, *New England J. Med.*, 224: 108, 1941.
113. FINE, J., AND SEARS, J. B.: The Prophylaxis of Pulmonary Embolism by Division of the Femoral Vein, *Ann. Surg.*, 114: 801, 1941.
114. STARR, A., FRANK, H. A., AND FINE, J.: The Venographic Diagnosis of Thrombophlebitis of the Lower Extremities, *J. A. M. A.*, 118: 1192, 1942.
115. DOUGHERTY, J., AND HOMANS, J.: Venography: A Clinical Study, *Surg., Gynec. & Obst.*, 71: 697, 1940.
116. HOMANS, J.: Thrombosis as a Complication of Venography, *J. A. M. A.*, 119: 136, 1942.
117. DE TAKATS, G.: Personal Communication.
118. JESSER, J. H., AND DE TAKATS, G.: Visualization of the Pulmonary Artery during its Embolic Obstruction, *Arch. Surg.*, 42: 1034, 1941.
119. LEVICHE, R., FONTAINE, R., AND FRIEDMANN, L.: L'infiltration stellaire est-elle justifiée dans l'embolie pulmonaire du point de vue physiologique et anatomo-pathologique?
120. TRENDLENBURG, F.: Ueber die operative Behandlung der Embolie der Lungenarterie, *Arch. f. klin. Chir.*, 86: 686, 1908.

121. MYSTROEM, G.: Experiences with the Trendelenburg Operation for Pulmonary Embolism, *Ann. Surg.*, 92: 498, 1930.
122. MUSTMANN, O., AND HALLERVORDEN, J.: Beobachtungen bei Trendelenburgschen Embolieoperationen, *Deutsche Ztschr. f. Chir.*, 245: 472, 1935.
123. LEWIS, I.: Trendelenburg's Operation for Pulmonary Embolism, *Lancet*, 236: 1037, 1939.
124. VALDONI, P.: Un Caso di Embolia Dell Arteria Pulmonare Guarito con L'embolectomia, *Policlinico (sez. prat.)*, 43: 911, 1936.
125. BARKER, N. W., NYGAARD, K. K., WALTERS, W., AND PRIESTLEY, J. T.: A Statistical Study of Post-operative Venous Thrombosis and Pulmonary Embolism. III. Time of Occurrence During the Post-operative Period, *Proc. Staff Meet., Mayo Clin.*, 16: 17, 1941.
126. MASTER, A. M., DACK, S., AND JAFFEE, H. L.: Postoperative Coronary Artery Occlusion, *J. A. M. A.*, 110: 1415, 1938.
127. PETTERSON, G.: Some remarks on the Indications for Trendelenburg's Operation in Reference to an Operated Case, *Act. Chir. Scandinav.*, 77: 163, 1935.
128. MYSTROEM, G.: Erfahrungen in drei nach Trendelenburg operierten Faellen von Lungenembolie, *Arch. f. klin. Chir.*, 152: 450, 1928.

## TOXEMIAS OF PREGNANCY

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The term, toxemia of pregnancy, comprises a group of pathologic conditions, some occurring only in pregnancy, e.g., hyperemesis gravidarum, eclampsia and impetigo herpetiformis; others occurring with or without pregnancy, e.g., acute yellow atrophy of the liver, polyneuritis, some dermatoses and psychoses. In the former group pregnancy is the exclusive cause of the disorder; in the latter, pregnancy represents only a predisposing though important etiologic factor. Hormonal imbalance, vitamin deficiency and dietary errors which are tolerated in the nonpregnant state, may not be tolerated because of the increased requirements of pregnancy.

Many authors restrict the term "toxemia of pregnancy" to a special group of disorders which usually occur in late pregnancy, are often combined, merging from one form into another, and which are obviously provoked by the same cause. These diseases, albuminuria, dropsy, preclampsia, and eclampsia of pregnancy, are the subject of the following discussion.

Eclampsia and the related toxemias have always been a puzzling and most difficult problem in obstetrical pathology. The striking similarity of uremic and eclamptic convulsions, the occurrence of albuminuria and edemas, and finally the predisposition of nephritic patients to eclampsia suggested the idea that eclampsia is only a special kind of nephritis or uremia. But even if this supposition had not been proved wrong, the cause of the nephritis would remain unrevealed.

The origin of the supposed renal insufficiency seemed to be discovered when autopsies of patients with eclampsia revealed dilated and tortuous ureters, changes attributed to pressure from the enlarged and heavy uterus. Further experiences and study proved that this assumption was entirely erroneous. Numerous investigations gave evidence that dilatation, elongation and hypotony of the ureters are normal hormonal reactions more or less pronounced in every pregnant woman. We know that this peculiar state of growth, succulence and hypotonia is not restricted to the uterus, but is a hormonally determined condition of all pelvic organs. Compression of the dilated ureters, mostly of the right one, is not rare. It constitutes a predisposition for pyelitis but never for eclampsia. The urinary findings and the whole clinical picture of urinary stasis caused by compression of the ureters are entirely different from those in eclampsia.

Changes found in the kidneys of pregnant women suffering from toxemia have been interpreted in entirely different ways in the passage of time. The variety of terms used to characterize the condition (kidney of pregnancy, nephropathia gravidarum, low reserve kidney, nephrosis of pregnancy) reflect the misinterpretations of the real condition. We find degenerative and vascular lesions in the kidneys without any sign of inflammation with comparatively good



kidney function. The renal concentration ability is not impaired and the non-protein nitrogen content of the blood remains within normal limits. There is no need for complicated explanations of the renal alterations in eclampsia. The anatomical findings and the clinical picture, particularly the sudden rise in blood pressure, the rapid development of excessive albuminuria, oliguria and even of complete anuria, the rapid regression of these alarming symptoms in cases showing improvement, and finally the usually complete return to the norm are unmistakable indications that sudden and violent spasms of the renal arteries constitute an etiologic factor in the toxemic condition.

It is no wonder that in an epoch of fascinating discoveries in bacteriology the cause of the toxemias of pregnancy has been sought in various specific infections. But all such investigations have resulted in failure.

The mystery of these toxemias seemed to be solved when Veit discovered that particles of fetal villi frequently break off, enter the maternal circulation and are deposited in various organs. He presumed that these tissue particles are dissolved by specific syncytiolysins and neutralized by antisyncytiotoxins. This theory that toxemia of pregnancy is caused by a lack of sufficient anti-syncytiotoxins gained much credence among obstetricians. The sensational pregnancy test of Abderhalden which stemmed from Veit's syncytiotoxin theory seemed to be an infallible proof of the correctness of this theory. Today both Veit's theory and Abderhalden's test are of historical interest only.

Other hypotheses based upon various discoveries in serology were also proved wrong. For example, the hypothesis that toxemias are caused by spermio toxins, or that eclampsia is some kind of allergic reaction and anaphylactic shock.

Comparative chemical, physicochemical, clinical and anatomical studies of pregnant women with and without toxemia resulted in the first valuable contributions to a potential solution of the problem. In this connection, the following findings may be mentioned:

(1) Zweifel's discovery of an increase in lactic acid in blood and urine of eclamptic patients. Further experience proved that this increase in lactic acid is a consequence of the eclamptic convulsions rather than a causative factor of the condition.

(2) Hasselbalch's and Gammeltoft's findings of an increased acidosis in eclampsia. Leimdoerfer, Novak and Porges had first shown a state of physiologic acidosis to exist in pregnancy. Characteristic of the condition is that the carbon dioxide combining power is decreased. In 1924 and 1933 Klasten reported interesting respiratory changes in patients with eclampsia. Some of these women had very deep but not frequent respirations (bathypnoic type), others frequent, but shallow respirations (tachypnoic type). Recently Plass observed that patients with toxemia do not get convulsions if the respiratory rate is lower than 14-16 per minute. It is obvious that increased acidosis is the cause of this increase in respiration and that the presence of acid metabolites plays a considerable rôle in the clinical picture of eclampsia. However, the real nature of these acid metabolites is unknown and it cannot be decided whether they cause eclampsia or are to be classified only as concomitants of the disease.

(3) Zangemeister's observation regarding the salt and water retention in pregnant women later confirmed by numerous investigators is of utmost importance. The tendency to salt and water retention becomes apparent after the fourth month of pregnancy and gradually increases toward the term. An attempt to explain this phenomenon will be made later.

A consequence of the water retention is a marked increase of the whole blood volume. But the increase does not involve all the constituents of the blood in the same degree. For instance, the increase in blood plasma amounts to 25 per cent, in the volume of the blood cells to 20 per cent, in hemoglobin only to 13 per cent. The water content is increased most. Thus we can speak of a hydremia, an edema of the blood in pregnancy. The blood cells are increased in number and volume, but their hemoglobin content is relatively low.

Due to this hydremia the specific gravity of the blood is diminished and the percentage of proteins in the blood is lessened. However, there exists not only a hypoproteinemia but also a change in the various blood proteins. The albumin-globulin ratio is greatly diminished (it is 2.6 in nonpregnant women, 0.81 in pregnant women at term, and 0.21 in patients exhibiting eclampsia). The fibrinogen content is increased. Thus, there exists a marked shift from the finely to the coarsely dispersed proteins.

(4) Neumann's and Hermann's findings in 1912 concerning an intense lipemia, lipidemia and particularly cholesterinemia, since confirmed by many others. As a consequence of these changes in proteins and lipids, the surface tension, the osmotic pressure and the colloidal stability of the blood are diminished and the sedimentation rate of the erythrocytes increased. On the other hand, the blood calcium is diminished.

(5) Hofbauer's observation that the acetylcholine content of the placenta which is high under normal conditions is markedly lower in toxemia. Since acetylcholine is a powerful vasodilating compound, its decrease in preeclampsia is significant. Hofbauer's findings are in accord with the previous discovery made by Spaeth and Eufinger of a lower cholin content of the blood in women with eclampsia.

(6) Kapeller's detection of the regular occurrence of histidine in the urine of normal pregnant women and its absence in patients with toxemia. Instead of histidine she found histamine in the latter cases. These findings are very remarkable but corroboration by other investigators is still lacking.

(7) Chunilal Mukherjee's assumption of an increased concentration of posterior lobe pituitary hormone in the blood of patients with toxemia. Confirmation of these also previously postulated but never exactly proved facts would be very helpful in satisfactorily accounting for such symptoms as the retention of water, hypertension and convulsions. It is a well known fact that an injection of pituitrin can easily provoke eclamptic attacks in a preeclamptic patient.

(8) Aschheim's and Zondek's findings of excessive levels of gonadotropic and estrogenic hormones in the organism. This is in pregnancy an assured fact, while the question of an increase in pituitrin is still controversial. The water

retentive power of estrogen and progesterone is certainly an important etiologic factor in toxemia of pregnancy.

Important clinical findings are:

(1) The already stressed tendency of pregnant women and particularly of those with toxemia to intra- and extracellular water retention.

(2) The tendency to vascular spasms demonstrated by Hinselmann and others on the blood vessels of the nails and the retina.

(3) The tendency to hypertension with sudden exacerbations inducing eclamptic convulsions.

(4) The occurrence of albuminuria which is one of the most constant symptoms of toxemia and apparently due to spasms of the renal vessels.

(5) Marked changes in cerebral activity, as revealed by encephalographic studies of Gibbs and Reid, Maltby and Rosenbaum, predisposing the patient to convulsions.

Valuable contributions to the whole problem can be traced to anatomical research work. Postmortem examinations revealed glycogen disappearance and fatty infiltration, necroses and hemorrhages in the liver, degenerative lesions in the kidneys, particularly in the renal tubules, edema and hemorrhages in the brain, thromboses and placental tissue emboli in the vessels of the lungs, liver, kidneys, brain and skin. Some of these changes are probably produced by intensive and long lasting vascular spasms, others by metabolic disorders developing under the influence of a disbalanced endocrine system.

Under the influence of the corpus luteum and later on of the placenta, marked changes take place in all the endocrine glands, particularly in the hypophysis, the thyroid and the adrenal cortex. There is no doubt that these changes are the main sources of the physiological as well as of the pathological processes in the pregnant organism.

At present, there are many authors who, like Strauss, regard the hypoproteinemia as the only factor responsible for all toxic phenomena. The hypoproteinemia alone or in combination with a higher sodium intake causes water retention in the tissues and in the blood, rise in blood pressure, and, if intensive enough, edema of the brain and convulsions. According to Strauss it is entirely superfluous to search for a toxic substance or hormone which should be responsible for the toxemia. Many authors assume that the hypoproteinemia in pregnancy and especially in eclampsia is identical to the hypoproteinemia due to malnutrition. Consequently they recommend a high protein diet for the prophylaxis and plasma infusions for the treatment of toxic disorders.

Though we do not deny the gratifying effect of plasma infusions on toxic conditions, we cannot subscribe to the idea that the hypoproteinemia in pregnancy is due to an insufficient protein intake. We have to consider that the hypoproteinemia is a normal condition in pregnancy, at least to a certain degree. It is very probable that such a constant pregnancy reaction may have a physiological significance. It would not appear difficult to find out the meaning of this reaction.

The fetal villi of the human hemochorial placenta dip into the maternal blood

without any protective diaphragm and their nutritive epithelial lining would be impaired if the conditions of the maternal blood were far different from theirs. The integrity of the villi will be preserved best and they can accomplish their function, i.e., the absorption, transformation and assimilation of nutritive substances from the maternal blood, more easily if the physical condition of the villi and on the other hand that of the maternal blood and tissues are similar. As the fetal tissues are characterized by their abundance of water, the maternal tissues must also retain more water to obtain a degree of turgescence similar to that of the fetal tissues. The retention of water is inseparable from the retention of corresponding amounts of salts. Therefore, the physiological hydremia, and thus hypoproteinemia means an adaption of the maternal organism to that of the fetus, whose tissues have a higher water content than those of the adult organism. The hypoproteinemia, the decrease of the finely dispersed proteins in favor of the coarsely dispersed proteins, and the lowering of the surface tension facilitate the flow of water and of nutritional material to the fetal blood, the colloidal stability of which is markedly higher.

However, the greater water content, the swelling and "rejuvenation" of the maternal tissues are not only needed for the undisturbed nutrition of the fetus but also for the softening, growth and expansibility of the maternal passages. These changes are indispensable for the maintenance of pregnancy as well as for delivery.

Consequently, the hypoproteinemia in toxemias is only an accentuation of a condition otherwise physiological in pregnancy. It is by no means identical with hypoproteinemias from other causes due either to an excessive loss in proteins or to an insufficient intake of proteins. It is an acknowledged clinical fact that toxemias are not diseases of undernourished but rather of well or even overnourished women. During the first world war eclampsia became very rare among the undernourished population of Central Europe and reappeared promptly in the usual percentage with the return to normal food conditions. It is well known that eclampsia is more frequent in young, well nourished, obese primigravidae with reactive endocrine systems than in old flabby multigravidae with an exhausted organism.

As far as we can judge from our present knowledge, the toxemias of pregnancy are the consequences of excessive activity of some endocrine glands, i.e., they are caused by an exaggeration of otherwise normal and useful pregnancy reactions. A hyperfunction of the adrenal cortex, which regularly hypertrophies in pregnancy, of the placenta and of the posterior lobe of the hypophysis are probably the factors responsible for the marked water and salt retention. The antagonistic function of the thyroid gland which promotes the excretion of water is apparently insufficient to balance the excessive activity of the adrenal cortex and its synergists.

The attempt to explain the vascular spasms which are not less characteristic for the toxemic condition than the hypoproteinemia is more difficult. The theory of J. Hofbauer, of Anselmino and Hoffmann and others who trace the spasm to an excessive production of pituitrin seems more plausible than the

assumption of hyperguanidinemia or hypocalcemia given by other investigators as causative factors.

The present usual prophylaxis and treatment of the toxemias is directed against their troublesome symptoms since it is not possible to treat the hyperactivity of the endocrines causing the condition. Avoidance of overfeeding during pregnancy, bedrest, salt free diet, sedatives and narcotics, hypertonic glucose and plasma infusions are our best suggestions and agents against these dangerous conditions.

#### SUMMARY

(1) The clinical features of the eclampsia and related toxemias can be explained by a combination of two factors: (a) An excessive retention of water and salt; (b) Vascular spasms.

(2) The water and salt retention is probably due to an excessive production of adrenal cortex hormone, estrogen and pituitrin. The vascular spasms are of the consequence of an excessive pituitrin action.

(3) Within limits the retention of water and salt is necessary for the integrity of the placental villi and the adaptation of the birth canal to the requirements of pregnancy and delivery.

(4) The usual prophylaxis and treatment of the toxemias are not causal but symptomatic. An effort is made to reduce the pregnancy reactions to their normal level and to correct their noxious consequences.

#### REFERENCES

- ABDERHALDEN, E.: Die Abderhalden'sche Reaktion. ed 5. Berlin, J. Springer, 1922.
- ANSELMINO, K. J., AND HOFFMANN, F.: Nachweis der antidiuretischen Komponente des Hypophysenhinterlappenhormons und einer blutdruckssteigenden Substanz im Blute bei Nephropathie und Eklampsie der Schwangeren. *Klin. Wehnschr.*, 10: 1438, 1931.
- ANSELMINO, K. J., AND HOFFMANN, F.: Ueber die Entstehung der Nephropathie und Eklampsie der Schwangeren durch Ueberfunktion des Hypophysenhinterlappens. *Klin. Wehnschr.*, 10: 1442, 1931.
- EUFINGER, H., AND GOTTLIEB, J.: Schwankungen im Blutcholinspiegel im Verlaufe der normalen Schwangerschaft und bei Schwangerschaftstoxikosen, 12: 1981, 1933.
- GIBBS, F. A., AND REID, D. E.: The Electroencephalogram in Pregnancy. *Am. J. Obst. & Gynec.*, 44: 672, 1942.
- HASSELBALCH, K. A., AND GAMMELTOFT, S. A.: Die Neutralitätsregulation des graviden Organismus. *Biochem. Ztschr.*, 68: 207, 1915.
- HERMANN, E., AND NEUMANN, J.: Ueber den Lipoidgehalt des Blutes normaler und schwangerer Frauen sowie neugeborener Kinder. *Biochem. Ztschr.*, 43: 47, 1912.
- HINSELMANN, H.: Eklampsieforschung. *Monatschr. f. Geburtsh. u. Gynäk.*, 59: 56, 1922.
- : Die Capillarstroemung bei der Eklampsie. *Arch. f. Gynäk.*, 116: 443, 1922-1923.
- HOFBAUER, J.: New orientation on etiology of toxemia of pregnancy and some practical applications. *West. J. Surg.*, 49: 615, 1941.
- KAPELLER-ADLER, R.: Histidine metabolism in normal and toxemic pregnancy. Excretion of histidine in normal urine and in urine of patients with toxemia of pregnancy. *J. Obst. & Gynaec. Brit. Emp.*, 48: 141, 1941.
- : Significance of isolation of histamine from urine in toxemia of pregnancy. *J. Obst. & Gynaec. Brit. Emp.*, 48: 155, 1941.
- KLAFTEN, E.: Die Hyperventilationseklampsie. *Zentralbl. f. Gynäk.*, 57: 1445, 1933.



- LEIMDOERFER, A., NOVAK, J., AND PORGES, O.: Ueber die Kohlensäurespannung des Blutes in der Graviditaet. *Ztschr. f. klin. Med.*, 75: 301, 1912.
- MALTBY, G. L., AND ROSENBAUM, M.: Relation on cerebral dysrhythmia to eclampsia. *Proc. Soc. Exper. Biol. & Med.*, 50: 10, 1942.
- MUKHERJEE CHUNILAL: Posterior pituitary factor in toxemias of pregnancy. *J. Obst. & Gynaec. Brit. Emp.*, 48: 586, 1941.
- NEVERMANN, H.: Kapillarbeobachtungen bei Eklampsie u. Schwangerschaft. *Zentralbl. f. Gynäk.*, 44: 1425, 1920.
- : Zur Ursache des Schwangerschaftsangiospasmus. *Deutsche med. Wehnschr.*, 49: 612, 1923.
- PLASS, E. D.: Eclampsia at the University Hospital, 1926 to 1941. *J. A. M. A.*, 119: 872, 1942.
- SPAETH, B.: Untersuchungen ueber die Veraenderung des Blutcholingehaltes in der normalen und toxischen Schwangerschaft. *Monatschr. f. Geburtsh. u. Gynäk.*, 102: 167, 1936.
- STRAUSS, M. B.: Observations on etiology of toxemias of pregnancy, etc. *Am. J. M. Sc.*, 194: 772, 1937.
- : Observations on etiology of toxemias of pregnancy, etc. *Am. J. M. Sc.*, 195: 723, 1938.
- : Observations on etiology of toxemias of pregnancy, etc. *Am. J. M. Sc.*, 196: 188, 1938.
- : Toxemias of pregnancy; types and treatment. *Am. J. Obst. & Gynec.*, 38: 199, 1939.
- : The toxemias of pregnancy. *New York State J. Med.*, 40: 810, 1940.
- VEIT, J.: Die Verschleppung der Chorionzotten (Zottendeportation). Ein Beitrag zur geburtshilffichen Physiologie und Pathologie. Wiesbaden J. F. Bergmann, 1905.
- ZANGEMEISTER, W.: Der Hydrops gravidarum, sein Verlauf und seine Beziehungen zur Nephropathie und Eklampsie. *Ztschr. f. Geburtsh. u. Gynäk.*, 81: 491, 1919.
- : Die puerperale Eklampsie. *Deutsche med. Wehnschr.*, 47: 549, 1921.
- ZWEIFEL, P.: Zur Aufklaerung der Eklampsie. *Arch. f. Gynäk.*, 72: 1, 1904 and *Arch. f. Gynäk.*, 76: 537, 1905.

## ARREST BY PENICILLIN OF TWO CASES OF SUBACUTE BACTERIAL ENDOCARDITIS; DUE RESPECTIVELY TO AN ANAEROBIC STAPHYLOCOCCUS, AND TO STREPTOCOCCUS VIRIDANS

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The objects of reporting these two cases of subacute bacterial endocarditis arrested by modern chemotherapeutic methods are manifold. It seemed important to give practitioners exact details of the methods and technique employed in making the diagnosis of subacute bacterial endocarditis, in recovering the organism from the blood, in culturing it, and in treating the patient with penicillin alone, or, as in the second case herewith reported, with penicillin plus heparin. The first case reported is also interesting because of the isolation from the blood of the patient of a Gram positive anaerobic staphylococcus never previously reported as associated with subacute bacterial endocarditis. This emphasizes the importance of employing anaerobic cultural methods in addition to the usual blood culture technique, especially in those instances in which previous attempts to recover an organism in clinically active subacute bacterial endocarditis have failed. The bacteriologic methods are given in some detail, and a description of the staphylococcus anaerobius is incorporated. It should be added that it is not enough merely to have a sufficient supply of penicillin, with or without heparin; one must learn how to use these new compounds if one wants to have the highest percentage of successful results. The report therefore includes an account of the difficulties in diagnosis and in therapy which were encountered in both patients, and how they were overcome, with the final satisfactory arrest of a disease which in the past has given such discouraging results.

Until recently subacute bacterial endocarditis has been an almost uniformly fatal disease. One of us has seen clinical cases since his medical student days (over forty years ago) when Professor Delafield (1) demonstrated such cases in his clinic. Several hundred cases have come under observation in hospital practice, in the army medical service during World War I, and in civilian practice, and although active treatment of various kinds was instituted in most cases, only a very few were arrested. There seemed to be some improvement in the percentage of recoveries after the sulphonamides were introduced into the therapy, but the really encouraging results appeared only after penicillin administered in very large doses was instituted as a specific remedy in the treatment of subacute bacterial endocarditis with bacteremia. Dr. E. Libman (2), who has probably had the largest clinical experience in this disorder, gave the percentage of spontaneous recoveries as not over 4 per cent for the era preceding the sulphonamides and penicillin. Recently Dr. Leo Loewe (3) has observed and treated a consecutive series of 53 unselected cases and has reported only 26 per cent failures, and 74 per cent successes in arresting the disease. As the authors have had the exceptional opportunity of seeing several of these cases with Dr. Loewe, some even before treatment, they have become convinced that

for the first time the medical profession has a specific remedy which will arrest a considerable proportion of patients suffering from a disease which previous to the penicillin era was almost uniformly fatal, even in the hands of the most experienced internists. It is hoped that by employing other measures, e.g., bacteriophage, para-amino hippuric acid, etc., that the percentage of arrested cases and of recovered cases may become even better.

Case 1. (Adm. 517313.) *Valvular deformity, mitral stenosis and subacute bacterial endocarditis due to staphylococcus anaerobius, treated with 2 courses of penicillin alone, totalling 5,200,000 units.* A 44-year old housewife and school teacher was admitted to the semi-private pavilion of The Mount Sinai Hospital, March 2, 1944, with a 15-month history of malaise, weakness, non-productive cough, episodes of painful finger tips and calf tenderness, and a persistent low-grade fever with spikes to 104°F.

The patient was apparently well until December 1942 when she developed a sore throat, cough, fever to 104°F., associated with malaise and weakness. She recovered from these acute symptoms in two weeks' time. From December 1942 to March 1943 she complained of continued malaise and weakness with occasional temperature rises to 103°F. One morning in March 1943 while at home, she had a sudden attack in which her mouth became twisted, she could not speak, her right arm became weak and she dragged her right foot. This episode, confirmed by her husband, occurred while she was going to the bathroom and lasted about 5-10 minutes. After this hemiplegic attack, she began to complain of paraesthesias of the right half of the body which have persisted until the present date.

From March to June 1943 she ran an irregular fever of 102°F. to 104°F., lost 15 to 20 lbs. in weight, had a persistent cough and developed bouts of anorexia and vomiting. In June 1943 she was studied at The Mount Sinai Hospital Consultation Service and a diagnosis of chronic cardio-vascular disease with mitral stenosis and insufficiency was made. Subacute bacterial endocarditis was suspected but this diagnosis was not made at that time.

Because she did not improve, she was subsequently hospitalized in September 1943 at the Graduate Hospital in Philadelphia, where a diagnosis of subacute bacterial endocarditis was made, although repeated blood cultures were negative. She was discharged unimproved. When she presented herself on admission to The Mount Sinai Hospital in March 1944, in addition to the above complaints she gave a 2 to 3 months' history of tender, painful spots in her finger tips, and calf muscle tenderness that lasted from several days to 2 to 3 weeks and then cleared up spontaneously. At no time had she had signs of left heart failure. In her past history, the patient had had no severe illness; she had no knowledge of an attack of rheumatic fever or chorea.

*Examination:* The patient was a fairly well-developed, moderately well-nourished middle-aged, somewhat apprehensive white woman, slightly dyspneic but not orthopneic. The temperature was 102°F., pulse, 120, respirations, 38. The head, eyes, ears, nose and throat showed no abnormalities. No petechiae were seen. The heart presented a normal sinus rhythm. The heart was slightly enlarged to the right and left with a systolic and a presystolic murmur at the apex. The blood pressure was 110 systolic and 50 diastolic. Fluoroscopic examination of the chest revealed a heart as seen in advanced mitral stenosis. The left auricle was markedly enlarged. The lungs were normal to percussion and auscultation. The neck veins were slightly distended but no hepato-jugular reflex could be demonstrated. There was no ankle edema. Abdomen: The liver and spleen were palpable 1-2 fingers' breadths below the costal margin in the mid-clavicular line, the liver edge being smooth and slightly tender. The skin was negative. The extremities showed no abnormality. She complained constantly of numbness and sensation of tingling on the entire right side of the body from scalp to toes. Neurological examination revealed slight ptosis of the right eyelid and right facial asymmetry, hyperactive deep reflexes on the right side with a right ankle clonus and suggestion of a right Babinski, an inconstant irregular tremor of the right upper extremity with some reduction in power of this limb. No objective sensory changes were found. She was depressed and apprehensive.

*Laboratory Data:* (March, 1944) Blood: Wassermann negative, urea nitrogen, 12 mg. per cent. Urine: Reaction acid, specific gravity 1012, albumin faint trace, sugar absent, many red blood cells, few clumps of white blood cells, occasional hyaline and granular casts. Sedimentation time 18 millimeters in 17 minutes. Blood culture taken on admission was reported negative 2 weeks later. Hemoglobin 50 per cent; red blood cells, 2,700,000; white blood cells, 7,250; segmented polymorphonuclear leucocytes, 76 per cent; non-segmented polymorphonuclear leucocytes, 8 per cent; lymphocytes, 16 per cent.

Admission diagnosis was subacute bacterial endocarditis, rheumatic heart disease (inactive) with mitral stenosis and insufficiency and mild chronic right heart failure, severe secondary anemia, hysterical phenomena, possibly a cerebral embolus.

*Course:* The patient's admission symptoms and febrile course continued with daily temperature spikes to 101°F. or higher. A second blood culture taken on the 6th hospital day was also reported as "no growth" after observation for 2 weeks.

As it was strongly felt from the patient's clinical manifestations that subacute bacterial endocarditis was present, it was decided to see whether a positive blood culture could be obtained by the administration of 1 cc. of adrenalin 1:1000 solution, administered subcutaneously, combined with splenic massage. This was done partly at the suggestion of Dr. Myron Prinzmetal (4), who in addition suggested that we precede the adrenalin injection by the oral administration of 1.5 grains of nembutal to prevent subjective complaints.

On March 13, 1944, the 12th hospital day, this procedure was carried out. The patient's previous temperature course was studied and the adrenalin was given at 3:45 p.m., the time when her daily temperatures reached their highest levels. It was decided to take blood cultures  $\frac{1}{2}$  and 1 hour after the administration of the adrenalin at which times it was expected that the drug would have its maximum effect. Cultures were consequently taken by the routine blood culture technique (See "Discussion" below) at 4:15 p.m. and at 4:45 p.m. at which times the patient's temperature was 101.2°F. and 102.4°F., respectively. Two weeks later these two cultures also showed no growth. At 6:00 p.m. that evening the patient experienced a shaking chill. Her temperature at the time was 103°F. One hour after the chill, the patient's temperature rose to 104.2°F. No blood culture was taken at this point because neither of us was notified of this reaction in time.

On March 14, an electrocardiogram showed regular sinus rhythm and wide and notched P waves,—an abnormality often observed in enlargement of the left auricle secondary to mitral valve involvement.

On March 16, a typical Osler Node was noted in finger pad of right ring finger. Urine showed many red blood cells, occasional white blood cells, many hyaline and granular casts. On March 20, a flat plate of the abdomen showed evidence of enlargement of the spleen. The left kidney was posited but normal in size and shape.

On March 21st, the 20th hospital day, the patient was still running a febrile course with almost daily temperature spikes to above 102.4°F., and evidence of embolization as shown by the Osler node in the right ring finger pad and many red blood cells in the urine.

It was decided to make another attempt to obtain a positive blood culture. In view of the preceding four negative blood cultures it was felt that if there was a bacteremia present it was not showing up in the cultures taken previously because there were too few organisms in the blood stream to be detected.

The blood culture technique was therefore modified to detect a sparse bacteremia, i.e., more blood was drawn for culture and all the blood drawn was used for inoculation of liquid media. The seeded media were incubated under anaerobic and microaerophilic conditions. It was felt that anaerobic conditions would be amply satisfied at the depths of the culture flasks as 125 cc. Erlenmeyer flasks were used and were filled with 100 cc. of culture broth. This gives a large volume of liquid with a relatively small surface exposed to the air, as the exposed liquid surface is situated in the neck of the flask which has a narrow diameter. As an added precaution for the anaerobiasis the surface of two of the five flasks used was sealed with a vaseline plug, after inoculations, to exclude surface contact with the atmosphere (See "Discussion" below).

The adrenalin technique was again employed. In view of the previous febrile rise fol-

lowing the administration of the drug the temperature was now taken at half hourly intervals and the patient carefully followed. One cc. of adrenalin (1:1000) was given subcutaneously at 4:00 p.m. The spleen was massaged gently for a few seconds. At 6:00 p.m. the temperature had risen to 102.8°F. and the first blood culture (using the new five flask method) was taken. By 7:30 p.m. the temperature rose to 103.4°F. and another blood culture was taken. At 8:30 p.m. the temperature reached 103.6°F. The patient did not as yet have a shaking chill. It was decided to wait to see if this would occur and a culture could then be taken during the chill. However, by 9:30 p.m. the temperature began to fall and at 11:00 p.m. it was 103°F., no chill having occurred. A blood culture was taken at this time to compare the bacterial state of the blood during the descent of the temperature with that of the ascent of the fever.

Seven days afterwards, growth first appeared in the vaseline-sealed flasks in the first of the 3 blood cultures. Within the next few days, growth was present in all five of the flasks of the first two cultures and in four of the five flasks of the last culture taken during the temperature descent. The organism found in pure culture was a gram positive anaerobic microorganism later identified as *Staphylococcus anaerobius* (Jungano 13, 15).

From March 28th until April 6th, her temperature continued to rise daily to 101°F. or above. During this period in addition to the previous enlargement of the liver and spleen, the kidneys were now palpable. The urine showed many red blood cells, albumin and occasional casts. Tender spots developed in the finger pads of the 4th and 5th fingers of the left hand which remained for seven days. Her hemoglobin during this time was 51 per cent, her white blood count was 9,650.

On April 7th, the 34th hospital day, the first of the two courses of penicillin was started. Her temperature peak that day was 102°F. After a 500 cc. whole blood transfusion, the penicillin was begun. It was administered by continuous intravenous drip in the dosage of 200,000 units daily dissolved in 1000 cc. of normal saline solution. The penicillin was continued by the intravenous route for 5 days but this had to be changed to the intramuscular route of administration because the patient developed marked signs of retention of fluid despite digitalis and ammonium chloride. From the 7th to the 13th penicillin day, inclusive, the drug was given every 2 hours intramuscularly with a total daily dosage of 200,000 units. The calcium salt of penicillin used throughout was supplied by Messrs. Chas. Pfizer and Company, Brooklyn, N. Y. with the authorization of Dr. Chester S. Keefer of the National Research Council. The patient received a total of 2,600,000 units of penicillin during this first course of treatment.

Although the patient's temperature came down, she still had occasional daily fever rises to 101°F. or above. On the second day after starting penicillin, the patient developed left upper quadrant pain strongly suggestive of a splenic infarct. On the fourth day a small petechia was noted in the left lower conjunctiva. Ankle and sacral edema became very marked and so the patient's fluid intake was limited to 500 cc. daily. On the 7th penicillin day therapy was changed to the intramuscular route and a blood culture was taken because of the continuance of embolic phenomena. This culture, taken with clarase, said to be a penicillin inhibitor, showed no growth after observation for two weeks. Nevertheless, the patient continued to show embolic phenomena as evidenced by the development of a red, painful, tender Osler node on the right hypothenar eminence, and the passage of grossly bloody urine. On April 20th, the 48th hospital day, the first course of penicillin was completed. On this day the patient developed fluid in both chests and the left chest had to be aspirated on two occasions. A blood culture taken at this time, also with clarase, later proved to be negative.

On April 24th, temperature was 100°F. The patient developed a macular rash on the forehead and a maculo-papular rash on the left thigh which disappeared within 48 hours. This may have been a toxic effect due to the penicillin. There were no other toxic symptoms which could be ascribed to the penicillin.

On May 17, 1944, three blood cultures taken again with the modified technique and using the same adrenalin procedure were negative. Although blood culture was negative, the



patient was still running a temperature between 101°F. and 102°F. every day, so that on June 2, 1944 a second course of penicillin therapy was begun. The dose was 200,000 units a day administered *intramuscularly*. This was continued in doses of 25,000 units every 3 hours for 13 days. At the end of this time the patient's temperature was within the normal range, and she was discharged June 21, 1944.

Since her discharge she has had no sign or symptom of subacute bacterial endocarditis, i.e., no chills, fever, sweating, or embolic phenomena. Unfortunately, during November of 1944 without known cause, she developed a marked depression for which she was hospitalized on the Neurological Service of The Mount Sinai Hospital December 9, 1944. A blood culture, taken December 10, 1944, using the adrenalin procedure and the modified blood culture technique, showed no growth. No evidence of active subacute bacterial endocarditis could be found at this time.

TABLE 1  
*Reports of Blood Cultures in Case 1*

| DATE   | TECHNIQUE* | REPORT                    |
|--------|------------|---------------------------|
| 3/2/44 | R          | No growth                 |
| 3/7    | R          | " "                       |
| 3/13   | R          | " "                       |
| 3/13   | R          | " "                       |
| 3/21   | M          | Staphylococcus anaerobius |
| 3/21   | M          | Staphylococcus anaerobius |
| 3/21   | M          | Staphylococcus anaerobius |
| 4/13   | R          | No growth                 |
| 4/20   | R          | " "                       |
| 4/27   | R          | " "                       |
| 5/4    | R          | " "                       |
| 5/11   | R          | " "                       |
| 5/17   | M          | No growth in 3 cultures   |
| 5/31   | R          | No growth                 |
| 9/23   | R          | " "                       |
| 12/10  | M          | " "                       |

\* R = Routine blood culture technique.

M = Modified blood culture technique.

The subacute bacterial endocarditis has now been arrested for over 6 months. The accompanying figure 1 illustrates the temperature curve, the dosage and duration of the treatment with penicillin, blood counts, blood cultures, transfusion, non-specific medication, and other pertinent clinical data.

#### DISCUSSION

The organism isolated from the blood stream in this case has not been previously described as associated with a subacute bacterial endocarditis and has therefore been considered worthy of presentation. In a review of the bacteriology of endocarditis up to 1939, Shilling (6) cited 26 organisms as the causative agents. Since then, several other organisms have been added to the list, but as far as we could determine, all staphylococci previously isolated grew well under ordinary atmospheric conditions.

*Blood culture technique:* The routine blood culture technique at The Mount Sinai Hospital consists of drawing 23 cc. of blood from an antecubital vein of the patient and inoculating it



while at the bedside into seven culture media. Seventeen cubic centimeters of blood are inoculated into liquid culture media, that is, 5 cc. into each of three 125 cc. Erlenmeyer flasks each containing 100 cc. of broth, the first plain veal infusion broth, pH 7.4, the second 2 per cent dextrose-veal infusion broth, pH 7.4, and the third 10 per cent tomato extract-veal infusion broth, pH 7.6, and 2 cc. into a tube containing 10 cc. of Smith-Noguchi's cooked liver broth, pH 7.4, which is sealed with 2 cc. of sterile petrolatum. The other six cubic centimeters of blood is used to make three pour plates by mixing 2 cc. of blood with each of two tubes containing 12 cc. of 2 per cent dextrose veal infusion agar, pH 7.4 and one tube containing 12 cc. of plain veal infusion agar, pH 7.4 (7, 8). Each day Gram stains are made of samples from the flasks and each flask is subcultured aerobically and anaerobically by transplanting 2 to 3 cc. into a tube containing 10 cc. of 1 per cent dextrose-infusion broth and 2 to 3 cc. into a tube of cooked liver broth sealed with sterile petrolatum. For the purposes of initial isolation, blood cultures from suspected cases of subacute bacterial endocarditis are incubated in an atmosphere of increased carbon dioxide tension obtained by placing the culture in a glass jar into which a lighted candle is placed and then fitted with petrolatum sealed glass cover (9). This gives an atmosphere of approximately 3.5 per cent carbon dioxide. Some organisms, e.g., *Hemophilus influenzae*, *Brucella*, *Streptococcus viridans*, and gonococci grow better and faster under these conditions.

The efficiency of this blood culture technique has been repeatedly demonstrated by the high percentage of positive cultures obtained in diseases known to be associated with bacteremias, e.g., 95.5 per cent positive findings in cases of subacute bacterial endocarditis which came to autopsy (10) and 96.7 per cent positives in cases of lateral sinus thrombosis (11).

In our Case 1, however, the blood cultures were repeatedly negative despite the clinical picture of activity. We attributed this to the possibility that either the organisms in the circulating blood were too small in number to be detected by the means employed and/or that they were too fastidious to grow under the conditions offered. An attempt to eliminate these difficulties as much as possible was made according to the following principles: First, adrenalin was given before the blood culture was taken and the spleen cautiously massaged with the idea of increasing the number of organisms in the circulating blood (4). Then more blood was drawn for culturing. All the blood that was drawn was used for inoculation of liquid culture media. Fluid media may be considered more "sensitive" in detecting a small number of organisms in a given inoculum than solid media. Secondly, we improved the environmental conditions by using more of the enriched culture media, by placing the flasks in an atmosphere of increased carbon dioxide tension and by covering the surface of two of the culture flasks with petrolatum. The latter, by completely excluding contact with the atmosphere, increases the degree of anaerobiosis in the medium and thus would favor the growth of a possible anaerobe in the blood.

*The modified blood culture technique:* Thirty cubic centimeters instead of the usual 23 cc. of blood was drawn. Five flasks of media were used for the culture. Six cubic centimeters was dispensed into each of two flasks of 10 per cent tomato extract-veal infusion broth, two flasks of 2 per cent dextrose-veal infusion broth and one flask of plain veal infusion broth. After inoculation, one tomato-extract and one dextrose broth flask was layered with 5 cc. of melted sterile petrolatum which had been allowed to cool to near the solidifying point before adding. All the flasks were incubated in a petrolatum sealed candle jar which produces a 3.5 per cent carbon dioxide atmosphere. No pour plates were included in this

blood culture. Later we drew 4 cc. of blood additional and added therewith two pour plates to the culture.

A small number of organisms inoculated into liquid culture media have a better chance of surviving and growing in most instances than the same number cultured in solid media. Due to the sudden change of environment, the mortality of bacterial cells inoculated into solid media is higher. It seems from experimental estimates, according to Shwartzman (12), that one must have at least 5 bacterial cells in the 2 to 3 cc. of blood used in a pour plate in order to obtain at least one colony in a solid medium blood culture. This is not the case with fluid culture media. Here the environmental change is less drastic. Therefore, when one obtains growth in a flask of fluid medium, it may be assumed that there may have been present initially not more than one bacterial cell in the 5 to 6 cc. of blood used to inoculate the medium.

#### BACTERIOLOGY

*Isolation:* The organism was isolated from the blood of the patient on three separate occasions on March 21st, 1944. Growth was first observed on the 7th day in one of the vaseline sealed tomato broth flasks of the first blood culture taken. Within the next four days, growth was found in all the media inoculated of the first and second blood cultures taken while the temperature was rising and in four of the five flasks of the third blood culture taken when the fever curve was on the decline.

*Gram positive coccus:* When this organism was first isolated it had the characteristics of a "rough" phase organism. The growth on a blood agar plate after 48 hours incubation at 37°C. in a nitrogen gas anaerobic jar consisted of minute, grayish, dry granular colonies measuring less than 1 mm. in diameter. Under the microscope the surface of the colony appeared dull, the edge irregular. The colonies were firm in consistency and were removed from the medium with great difficulty. The colonies produced neither green pigment nor hemolysis on blood agar. The organisms from these colonies did not enter into suspension in saline but precipitated spontaneously. Growth at first, best in serum-brain-beef-heart infusion broth, was granular and sedimented to the bottom of the culture tube producing a minimal diffuse clouding.

For many weeks subsequent to initial isolation these organisms were fastidious in their growth requirements. They were strictly anaerobic in all subcultures. Serum or blood and moisture were required for growth. The cultures were kept by transferring to freshly prepared blood agar plates every 48 to 72 hours. Later, the strain could be maintained by subculturing every 7 to 10 days.

After 8 weeks of subculturing, the blood agar plate cultures began to show occasional greyish-white colonies which measured up to 1.5 to 2.0 mm. in diameter. Under the microscope, the surface appeared even and the edge entire, without projections. The colonies were moist in appearance and soft and moderately butyraceous in consistency. In dextrose-serum broth and in brain-beef-heart infusion broth, these organisms produced a diffuse clouding which only after several days settled to the bottom of the culture tube leaving a fine precipitate along the dependent sides of the tube. These colonies still did not produce any greening or hemolysis on the blood agar plates. The organisms were more easily susceptible in saline, but a heavy saline suspension was not characteristic.

*Morphology and staining characteristics:* The micro-organism was very small occurring as spheres, varying in size from 0.5 to 0.6 microns, grouped singly, in pairs or short chains, but chiefly as irregular masses. They were non-motile, non-spore forming and non-encapsulated. They stained consistently strongly Gram positive on initial isolation, but after several months of subculturing it was noted that they became more easily decolorized by

Gram's method. They stained readily with methylene blue and showed no metachromatic granules. Using the Ziehl-Neelsen technique they were not acid-fast.

*Physical growth requirements:* Optimum growth occurred at 37°C. under strictly anaerobic conditions. After initial isolation cultures were kept in a pressure jar from which the air had been evacuated and replaced by nitrogen under 7 to 8 lbs. of pressure. Growth did not occur under normal atmospheric conditions or at a 10 per cent carbon dioxide tension. The organisms did not withstand exposure to 60 C. for 30 minutes. No growth occurred below 22°C.

*Cultural requirements:* For several weeks to months after initial isolation, the organisms required serum or blood containing medium. Later, however, growth was accomplished in dextrose veal infusion broth or on 2 per cent glucose agar, but growth here was always scanty. The growth in dextrose-veal infusion broth at first produced a fine turbidity—which later becomes more granular with the settling of a fine sediment to the bottom of the tube. Good growth occurred on brain-beef heart infusion agar (Difco).

*Cultural reactions:* No greening or hemolysis of blood was ever noted, blood agar plates remaining unchanged after 2 weeks' growth. No acid or gas was produced in dextrose-veal infusion broth. There was no liquefaction of gelatin. Milk remained uncoagulated, and unacidified. Nitrites were not produced from nitrates and no indole or gas was produced in peptone water. No change was produced in neutral red broth. Saccharose was strongly fermented, glucose slightly, lactose, mannite and sorbitol were not attacked. All fermentation reactions were observed for a period of 14 days.

*Pathogenicity:* This was tested for mice and guinea pigs. One cubic centimeter of a heavy suspension of the organisms was injected intra-peritoneally into mice and guinea pigs, but all the animals remained alive and well after being followed for 8 weeks. Small abscesses which healed spontaneously in a few days were produced by intradermal and subcutaneous inoculation; and from which the organism was subsequently recovered in pure culture.

*Habitat:* The organism was first isolated and described by Jungano (13) in Paris in 1907. He obtained it from a case of cystitis. Prevot (14) found the organism in the pus from suppurative tonsillitis. Bergey (15) and Weinberg (16) list the natural habitat of the organism as the buccal cavity, conjunctiva, urinary tract, urethra, intestine, and female genital tract.

*Immunology:* The organisms were self-agglutinating and therefore agglutination studies with the patient's serum and with other known anti-sera were unsatisfactory.

*Penicillin sensitivity:* There was complete inhibition of growth with 3 Oxford units of penicillin, i.e., the organism was 3 times as resistant as the standard test organism, *Staphylococcus*, strain H.

Case 1 is interesting from a bacteriologic and therapeutic standpoint. Bacteriologically, of special interest is the isolation from the blood stream of a pyogenic, strictly anaerobic staphylococcus, which has been described in relation to suppuration in the nasopharynx, but never previously reported as associated with subacute bacterial endocarditis. Although the organism was isolated from the blood during only one evening, we feel that this organism can safely be ascribed to be the causative agent, in view of the clear cut clinical picture of subacute bacterial endocarditis, because; a) it was isolated on three separate occasions several hours apart, b) it was found in all the media, in pure culture, on two occasions in 5 flasks and in 4 of 5 flasks on the third occasion, and c) because of the rarity of the organism. In view of this it is unlikely that this organism is a contaminant.

Therapeutically this case is interesting because it represents an instance of



subacute bacterial endocarditis, due to an anaerobic staphylococcus—arrested now for over 6 months by the use of penicillin alone.

Case 2. (Adm. #516453) *Chronic rheumatic cardiovascular disease with mitral stenosis and insufficiency, and aortic regurgitation; subacute bacterial endocarditis due to streptococcus viridans & arrested with 4,200,000 units of penicillin combined with heparin.*

*History:* A 36-year old female was admitted to the semi-private pavilion of the Hospital on February 9, 1944 after 4 weeks of illness characterized by fever and malaise. She was referred by Dr. Mack Kohlenberg.

She was known to have had rheumatic heart disease since the age of 22 when she first came under the care of a staff physician (Dr. Irving Roth) of this Hospital. She had apparently been in good health until the preceding year, when she had a prolonged illness, called "pleurisy and pneumonia," at which time her heart was said to have been previously affected. She had had no rheumatic fever, chorea, growing or joint pains, scarlet fever or diphtheria, and she had led an active life.

In 1929 the patient was found to have a well-defined mitral stenosis, and the diagnosis of rheumatic heart disease was made. The patient was two months' pregnant and therapeutic abortion was advised. She underwent the procedure without medical complications, but following it she developed conspicuous emotional instability which has continued throughout the subsequent years.

During the following years the patient had frequent colds and sore throats, and bouts of fever as high as 103°F., lasting several days. Her first episode of congestive heart failure occurred in 1931 following a short period of fever. Since then the patient had bouts of fever, congestive failure, pulmonary infarction and broncho-pneumonia, so that she was bedridden almost half of every year except during the past 2 years. She had been digitalized on various occasions, but had not had any of the drug for over a year before admission, although exertional dyspnea and orthopnea were more or less persistent. An aortic diastolic murmur had been noted on one occasion, but was not heard at a later date.

The present illness began 4 weeks before admission, when she complained of generalized aches and pains, pain and tightness of her skin, and fever. This fever persisted longer than her usual attacks, and she became progressively worse, developing a non-productive cough, increase in dyspnea and orthopnea, nausea and vomiting. She had several teeth drilled but no extractions. Two blood cultures taken on the outside showed no growth.

*Examination:* On admission she appeared very ill. Her temperature was 100.6°F. She breathed easily only in the sitting position but was not cyanotic. There were no petechiae on the skin, conjunctivae, fundi or buccal mucosa. The tonsils were present, not acutely inflamed, and there was no adenopathy. There were signs of congestion at both lung bases. The heart was markedly enlarged, and hyperactive. The point of maximum impulse was found to be in the 5th intercostal space in the anterior axillary line. The rhythm was regular, rate, 120. There were systolic and diastolic murmurs at the apex. No murmurs were heard at the base. The blood pressure was 110 systolic and 70 diastolic. The liver and spleen were not palpable. There was no peripheral edema, and no clubbing of the fingers or toes.

*Laboratory data:* Blood studies: hemoglobin, 64 per cent; red blood cells, 3,650,000; white blood cells, 12,900. Polymorphonuclear leucocytes, non-segmented, 10 per cent; polymorphonuclear leucocytes, segmented, 80 per cent; lymphocytes, 6 per cent; and monocytes, 4 per cent. Examination of the urine showed no significant abnormal finding.

The diagnosis of rheumatic heart disease with mitral insufficiency and stenosis was made. The presence of subacute bacterial endocarditis was suspected.

*Course:* Two days after admission petechiae appeared on the soft palate and several crops appeared on the buccal mucosa and conjunctivae during the succeeding days. Several days later the spleen was felt two fingers below the costal margin. Two blood cultures taken the first and third days were then reported as showing streptococcus viridans (19 colonies per cc.). Thus the diagnosis of subacute bacterial endocarditis was confirmed.

The specific therapy was the continued use of penicillin and heparin as described by Dr. Loewe and carried out under his supervision. The penicillin is given in high dosage over a prolonged period. Dr. Loewe (3) believes that the heparin is an essential part of the treatment, although there is as yet no parallel control series of equally intensive penicillin therapy alone. The role that heparin plays is not definitely known: it is suggested that the heparin may facilitate the breakdown of vegetations, that by merely preventing further deposition of fibrin it may render the vegetation more permeable to the penicillin, and that heparin may be a coadjuvant to penicillin rather than merely an anticoagulant. The hep-

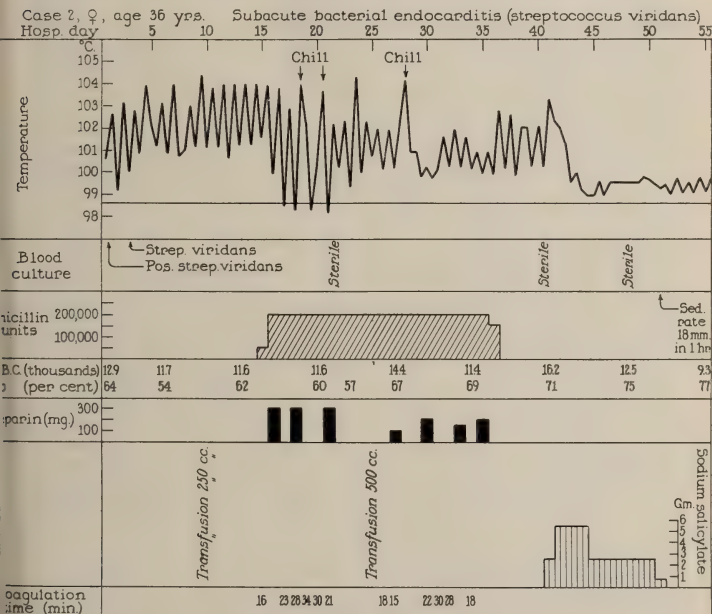


FIG. 2. (Case 2.) Chart showing temperature curve, blood culture reports, blood counts, coagulation time, penicillin administration, heparin administration, and other treatment during the patient's hospital stay.

arin is given in doses sufficient to raise the coagulation time, but not to more than 30 minutes. This is a far lower level than that first advocated by Kelson and White (5) and subsequently rejected by us and by others using this drug in subacute bacterial endocarditis, because of the high incidence of fatal hemorrhages.

Before the specific therapy was instituted (i.e. until the penicillin was administered) the patient's course was rapidly downhill. Her temperature rose to 103°F. The hemoglobin fell rapidly from 64 per cent to 47 per cent; it responded somewhat to blood transfusion. Heart failure became more severe; the liver enlarged to 4 fingers below the free costal mar-

gin, and sacral edema appeared. She failed to respond to digitalization; the nausea, vomiting and anorexia persisted.

On the fourteenth hospital day a 3 weeks' course of treatment was started. (This ran from Feb. 22 to March 14, 1944.) Penicillin was given intramuscularly because the congestive heart failure contraindicated the intravenous route. The dosage was 25,000 units every 3 hours in 3 cc. saline, amounting to 200,000 units per day, and a total of 4,200,000 units were administered during 3 weeks. The heparin was given subcutaneously. The heparin was supplied by Dr. Loewe. The subcutaneous deposit of heparin allows gradual release of the active substance to the body, and can be controlled if necessary by local application of ice, which prevents its too rapid absorption.

During the first week of therapy the patient had two very severe shaking chills, precipitating attacks of dyspnea and followed by temperature rise to 101°F. The exact etiology of these chills was not known. The possibilities included the liberation of large numbers of bacteria by the breaking up of vegetations due to therapy, spontaneous embolic phenomena, or drug reactions—either by the active ingredients themselves or due to some impurities such as pyrogenes in the preparations. In an attempt to evaluate the latter, and because the long period of repeated intramuscular injections was hard on the patient's morale, an attempt was made to give the medication intravenously using penicillin supplied by a different firm, and adding the intravenous heparin preparation "Liquaemin" (Heparin of La Roche). This was given in a total of 1000 cc. normal saline over 24 hours. On this regime, however, the patient had another chill, and despite limitation of oral fluid to 500 cc. per day, peripheral edema developed. Intramuscular therapy was resumed, and mercupurin was administered.

During the third week of therapy, the patient began to show some slight improvement. There were no further chills, the temperature remained at a slightly lower level. She began, however, to have left upper quadrant pain, and pain in the left shoulder on deep inspiration, presumably due to splenic infarction. Also an aortic diastolic murmur became audible, which persisted until discharge. There was an associated increase in pulse pressure. Aortic insufficiency seemed to have become established—whether entirely on a rheumatic basis or whether secondary to the bacterial endocarditis it was difficult to say.

During the first five days after completion of the treatment, the temperature remained elevated, signs of heart failure persisted, the patient showed psychotic manifestations. She was occasionally irrational and had recurrent "night terrors." Many of us were very pessimistic at this time. Dr. Loewe suggested that an exacerbation of rheumatic activity might be responsible for the symptoms,—this rather than bacterial endocarditis. This was supported by the fact that blood culture was sterile, and that the electrocardiograms showed prolonged P-R interval (0.26), very low voltage of the QRS, elevation of the R-T interval in leads 1 and 2 and semi-inverted T wave in leads 2, 3 and 4 indicative of either pericardial involvement or of myocardial damage.

Sodium salicylate was given (20 grs. every 4 hours) whereupon the temperature promptly dropped to between 99.2°F. to 99.8°F. The salicylate dosage was decreased after four days, and discontinued after ten days. During this time the patient showed marked improvement. The temperature remained flat. The sedimentation time approached 1 hour, the hemoglobin began to rise, the signs of cardiac failure disappeared, the appetite improved, and the patient had a general sense of well-being.

These signs of improvement all persisted until the patient's discharge from the hospital, which was over six weeks after the completion of the penicillin therapy.

During the remainder of her stay in the hospital the weekly blood cultures remained sterile, the hemoglobin was maintained between 70-75 per cent. The white blood cells ranged below 10,000 with a normal differential count. The sedimentation time was 55 and 56 minutes during those weeks.

The electrocardiogram showed the P-R interval 0.2 seconds; the QRS complex was higher; the R-T intervals in leads 1 and 2 were less elevated.

A search for foci of infection revealed three abscessed teeth and chronically diseased

tonsils. The teeth were extracted on April 21, 1944 while the patient received prophylactic penicillin, 12,500 units every 3 hours for 36 hours (150,000 units). A culture of the tooth revealed streptococcus viridans  $\alpha$ . A blood culture taken 2 days later showed no growth.

The blood cultures in this case were taken by the "routine method" described previously. The initial culture in each case was incubated under increased carbon dioxide tension. They became positive within 24-36 hours. The organism was the familiar streptococcus which produces a green pigment on blood agar plates. The blood cultures taken during penicillin therapy had "clarase" in all media. (Clarase is said to be an enzyme which inhibits the anti-bacterial action of penicillin.) All blood cultures were observed for two weeks.

Inasmuch as 9 months have elapsed since the specific treatment has been discontinued, we are inclined to believe that the condition has been arrested and she may remain permanently bacteria free.

#### SUMMARY

In this paper two cases of subacute bacterial endocarditis which were successfully arrested are reported in detail; the first by the use of penicillin alone in large doses, the second by the combined use of penicillin and heparin following the method used by Dr. Loewe. In the first case, the *Staphylococcus anaerobius*,—a strictly anaerobic micro-organism—was isolated from the blood stream by one of us with the assistance of the members of the Department of Bacteriology of The Mount Sinai Hospital. This organism has heretofore not been found in subacute bacterial endocarditis,—possibly because strictly anaerobic cultures are usually not employed in subacute bacterial endocarditis. The second case presented the familiar picture of chronic rheumatic cardiovascular disease with the typical phenomena of subacute bacterial endocarditis due to the streptococcus viridans  $\alpha$ . Neither patient has shown any evidence of a relapse of the bacterial endocarditis for 6 months and 9 months respectively since discharge from the hospital. Whether penicillin alone or penicillin plus heparin will ultimately prove to give the best therapeutic results in subacute bacterial endocarditis cannot be answered at the present time, as adequate comparable series of cases treated by the two methods have not been reported. In any case the value of penicillin in subacute bacterial endocarditis is confirmed.

We gratefully acknowledge our great indebtedness to Dr. Leo Loewe, to Dr. Gregory Schwartzman and Miss Cecele Hirschberger of the Department of Bacteriology, to Dr. William Frank and Dr. Naomi Kaplan, resident physicians, for their assistance, and to Dr. Chester S. Keefer of the Committee on Chemotherapeutics and Other Agents of the National Research Council, for providing the necessary penicillin.

#### BIBLIOGRAPHY

1. DELAFIELD, FRANCIS: Lectures on the Practice of Medicine. New York, J. T. Dougherty, 1898, p. 164.
2. LIBMAN, EMANUEL, and FRIEDBERG, CHARLES K.: Subacute Bacterial Endocarditis. New York, Oxford University Press, 1941.
3. LOEWE, LEO, ROSENBLATT, PHILIP, GREENE, HARRY J., and RUSSELL, MORTIMER: Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis. J. A. M. A., 124: 144, 1944.

- Also, LOEWE, LEO: The Combined Use of Penicillin and Heparin in the Treatment of Subacute Bacterial Endocarditis. *Canad. M. A. J.*, 52: 1, 1945.
4. PRINZMETAL, MYRON, AND OPPENHEIMER, B. S.: A Note to be published.
  5. KELSON, S., AND WHITE, P. D.: A New Method of Treatment of Subacute Bacterial Endocarditis Using Sulfapyridine and Heparin in Combination. *J. A. M. A.*, 113: 1700, 1939.
  6. SHILLING, M. S.: Bacteriology of Endocarditis with a Report of Two Unusual Cases. *Ann. Int. Med.*, 13: 476, 1939.
  7. SHWARTZMAN, G., AND GOLDMAN, J. L.: Streptococcus Hemolyticus Bacteremia. *Arch. Surg.*, 34: 82, 1937.
  8. SHWARTZMAN, G.: Food Accessory Substances in Bacterial Growth. *Proc. Soc. Exper. Biol. & Med.*, 22: 7, 42 and 44, 1924.
  9. HAYNES, E.: The Importance of Culturing Hemolytic Streptococci Under Increased Carbon Dioxide Tension. *Am. J. Clin. Path., Tech. Supp.*, 6: 55, 1942.
  10. LIBMAN, E.: Characterization of Various Forms of Endocarditis. *J. A. M. A.*, 80: 813, 1923.
  11. GOLDMAN, J. L., AND SHWARTZMAN, G.: Streptococcus Hemolyticus Bacteremia. *Ann. Otol., Rhin., & Laryng.*, 44: 961, 1935.
  12. SHWARTZMAN, G.: Immunological Aspects of Blood Invasion with Special Reference to Sinus Thrombosis. *Laryngoscope*, 49: 653, 1939.
  13. JUNGANO: Sur un staphylocoque anaérobie. *Compt. rend. Soc. Biol., Paris*, 59: 707, 1907.
  14. PRÉVOT, A. R.: Etudes de Systématique bactérienne. Cocci anaérobies. *Ann. Sc. Nat., Sér. 10, Bot.*, 15: 209, 1933. See Bergey, reference 15.
  15. BERGEY, D. H.: Manual of Determinative Bacteriology, ed. 5, Baltimore, Williams & Wilkins, 1939, p. 267.
  16. WEINBERG, M., NATIVELLE, R., AND PRÉVOT, A. R.: Les Microbes Anaérobies, Paris, Masson et Cie, Editeurs, p. 1020-1022, 1937.



# IMMUNITY TO TETANUS INDUCED BY A THIRD DOSE OF TOXOID THREE MONTHS TO FOUR YEARS AFTER BASIC IMMUNIZA- TION, BASED ON A STUDY OF 159 ALLERGIC CHILDREN\*

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To the pediatrician the problem of prophylaxis against tetanus is of particular importance. Tetanus may develop after receipt of a superficial scratch and even in persons lacking objective evidence of an injury for which no medical attention was sought. The routine injection of antitoxin in all cases of injury, a procedure carried out in the accident rooms of many hospitals and elsewhere, is obviously a dangerous practice when applied to allergic persons, especially those hypersensitive to animal serum. The frequency of allergic (hyperergic) shock among hypersensitive persons following the injection of serum is much higher than the reported incidence of 1 instance per 50,000 injections of serum in unselected cases. Numerous examples illustrating the inadequacy of passive immunization against tetanus have been encountered in civil and industrial practice. It is also of interest that there are no persons who have a natural immunity to tetanus analogous to the natural immunity to diphtheria possessed by some. The need for active immunization of all children especially allergic children against tetanus is obvious.

In my first report (1), on the appearance of tetanus antitoxin in the blood serum following 2 injections of 0.5 cc. each of combined alum-precipitated diphtheria and tetanus toxoids, it was shown that 94.6 per cent of a group of 186 allergic children attained a protective level of tetanus antitoxin when a critical level was considered as 0.01 American unit of antitoxin per cubic centimeter of blood. In a second study (2) a third, or "booster," injection of the combined toxoids was given to 65 of the same 186 children. Nine of these 65 children had failed to attain adequate immunity after the first two doses of the combined toxoids. The "booster" dose was administered three to fifteen months after the completion of basic immunization. In three subsequent communications (3-5) I reported the effect of the "booster" injection of 0.5 cc. of combined alum-precipitated diphtheria and tetanus toxoids or alum-precipitated tetanus toxoid alone given respectively to 31, 38 and 25 others of the 186 children described in the first report, 2, 3 and 4 years after the completion of basis immunization. The third, or "booster," dose of toxoid stimulated the production, in all instances, of an adequate titer for tetanus antitoxin. However, the "booster" dose of toxoid given 3 years after the completion of basic immunization

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F. G. Jones, of the Lilly Research Laboratories, gave technical assistance in this study.

The preparations of combined alum-precipitated diphtheria and tetanus toxoids and alum-precipitated tetanus toxoid used in this study were furnished by Eli Lilly & Co.

was always followed by a tetanus antitoxin titer which was higher and lasted much longer than that which developed after basic immunization or after the "booster" dose of toxoid injected 3 to 15 months, 2 and 4 years after basic immunization. The maximum antitoxin response following a "booster" dose of toxoid given 2 and 4 years after basic immunization was approximately parallel. The lowest antitoxin values obtained followed a "booster" dose of toxoid given 3 to 15 months after basic immunization. The results obtained in these studies reveal the observation that the intervals between the two basic doses of the combined toxoids and between these and the third dose have a direct influence on the antitoxin response. The longer the interval (up to three years) between the injections of toxoid the higher the antitoxin response.

In this communication, I am reporting the combined results of the published and unpublished data of a comparable study on the degree and duration of immunity after a third injection of 0.5 cc. of combined alum-precipitated diphtheria and tetanus toxoids or alum-precipitated tetanus toxoid alone, given 3 months to 4 years after basic immunization to 159 of the 186 children used in the study described in the first report. One hundred and fifty of the 159 children had attained adequate immunity after the two initial doses of the combined toxoids. These 150 children were divided into two groups. The 98 children in the first group were given a "booster" dose of 0.5 cc. of combined alum-precipitated diphtheria and tetanus toxoids, and the 61 in the second group were given a "booster" dose of 0.5 cc. of alum-precipitated tetanus toxoid alone. The creation of these two groups served a definite purpose which will be explained later. Since there was no appreciable difference in the immunities to tetanus induced by the combined toxoids and by the tetanus toxoid alone, the 150 children were treated as a single group for purposes of recording the antitoxin titers.

*Materials and methods.* The total number of samples of blood titrated for tetanus antitoxin from the 159 allergic children after the "booster" injection was 800. The dose consisted of a 0.5 cc. of the combined alum-precipitated diphtheria and tetanus toxoids or alum-precipitated tetanus toxoid alone and it was injected subcutaneously 3 months to 4 years after completion of the basic immunization with 2 doses of the combined toxoids. Seven hundred and forty-seven samples of blood had been titrated after the first two injections.

The tetanus toxin employed in the preparation of the combined alum-precipitated diphtheria and tetanus toxoids had a tetanus toxicity of 30,000 minimum lethal doses per cubic centimeter.

In this communication the tetanus antitoxin titers are expressed in American units.

*Levels of antitoxin which indicate immunity to tetanus.* It was assumed that, (6) to be of value, active immunization against tetanus must produce an antitoxin titer at least equal to that present in the blood after passive immunization with a prophylactic dose of 1,500 units of tetanus antitoxin. The minimal or critical protective value was arbitrarily placed at 0.1 unit of antitoxin per cubic centimeter of serum. After the prophylactic injection of tetanus antitoxin the

maximum antitoxin titer (0.1 to 0.25 unit) is reached on about the third day and most of the antitoxin has been lost by 11 days after the injection. The incubation period of tetanus is between 7 and 14 days or longer. The reason for occurrence of tetanus despite prophylaxis is obvious. However, the important fact that passive immunity is not comparable to active immunity must not be overlooked. Moreover, there is no scientific evidence to show that 0.1 unit of tetanus antitoxin is necessary to protect an actively immunized human subject against tetanus. Judging from the many reports in the literature (7), one may, with reasonable assurance, accept 0.01 unit of antitoxin per cubic centimeter of serum obtained through active immunization as the critical or protective level against tetanus in man and that level was so regarded in this study. Any value less than 0.01 unit per cubic centimeter was designated as inadequate or nonprotective.

*Tetanus antitoxin titer after the second and after the third dose of alum-precipitated toxoid.* Examination of the data revealed that for 150 patients titers determined after the second dose of combined toxoids were available for study with the 409 obtained at intervals of from 7 days to 2 years after the third dose. The values for antitoxin after the third dose of toxoid were higher in 378 of the 409 instances, lower in 7 and the same in 24. After the third dose the average increase in the antitoxin value was 15 times more and the average decrease 3 times less than the corresponding titers after the second dose.

From the data on 107 children it was found that when initial tests made within 2 months after the "booster" dose showed the antitoxin value to be higher, and in a few instances the same or even lower after the third dose than after the second, then tests performed 1 year later revealed not only that the drop of the titer was retarded after the third dose but that the antitoxin values were distinctly higher (a ratio of 10.7 to 1 or an average antitoxin titer of 0.355 unit as compared with 0.033 unit). The few instances mentioned above where the initial antitoxin values were the same or even lower after the third dose than after the second, occurred only in a few children injected with the "booster" dose from 3 to 15 months after basic immunization.

*Antitoxin titer within one month after the "booster" dose of toxoid.* Data from which to determine the effect of the "booster" dose of toxoid on the antitoxin response, with reference to the antitoxin titers obtained after the second and immediately preceding the third dose of toxoid were available for 152 patients. These patients were divided into three groups. Group 1 consisted of 9 children who failed to attain adequate immunity (an antitoxin level of 0.01 unit per cubic centimeter of serum) after the second dose of toxoid. Following the third dose of toxoid the titers ranged from 0.017 to 1 unit of antitoxin, or an average of 0.296 unit per patient. The increase in titer was from 6 to 33 times, or an average of 99 times, more than the control titer of 0.003 unit (inadequate immunity).

Group 2 consisted of 56 patients who had an adequate antitoxin level soon after the second dose of toxoid but whose titers some months later dropped to the level of 0.003 unit per cubic centimeter of serum. After the third dose of

toxoid the titers of these patients ranged from 0.1 unit to 5 units, with an average titer of 1.082 units. The increase in titer was from 33 to 1667 times, or an average of 350 times more than the control titer of 0.003 unit.

Group 3 consisted of 87 patients who also had an adequate antitoxin response soon after the second dose of toxoid but whose subsequent titers, obtained from 3 months to 4 years later though lowered, remained above the critical level of protection against tetanus. After the third dose of toxoid the titers for 84 of these patients ranged from 0.2 unit to 10 units of antitoxin with an average titer of 2.59 units as compared with an average titer of 0.036 unit immediately preceding the dose. The increase in titer ranged from 5 to 588 times, with an average of 82 times. (The data for the 3 remaining patients of this group were omitted in computing the averages because 2 of the patients had unusually high respective antitoxin titers of 30 and 40 units obtained within 1 month after the injection of the third dose of toxoid and for the third patient the control titer and the titer following the third dose of toxoid remained the same—0.05 unit of antitoxin).

For 5 of the children in the three groups antitoxin levels were also determined within one month of a fourth dose of 0.5 cc. of combined toxoids. The average antitoxin level of these 5 children after the second, third and fourth doses was 0.01, 0.134 and 0.23 unit, respectively. A fifth dose administered to 1 of these children resulted in an antitoxin titer of only 0.5 unit of antitoxin.

An analysis of the foregoing figures and of the other data, indicated that the antitoxin values obtained within one month after the administration of three or more doses of the combined alum-precipitated diphtheria and tetanus toxoids or alum-precipitated tetanus toxoid alone varied according to the antitoxin level present immediately preceding the "booster" injection and the nature of the immunity mechanism. When the titer was always maintained at the inadequate level (0.003 unit of antitoxin) after two doses of toxoid then the lowest average titer (0.296 unit) followed a third dose. When the titer dropped to the inadequate level subsequent to being adequate (0.01 unit or more of antitoxin) after two doses of toxoid then the average titer following a third dose rose to 1.082 units of antitoxin. When the titer was always maintained at the adequate level after two doses of toxoid then the titer following a third dose reached the highest antitoxin value, the average being 2.59 units of antitoxin. Moreover, for 3 of 5 children to whom it was desirable to administer a fourth or fifth dose of the combined toxoids, the antitoxin levels tended to become higher, but only within certain limits (0.5 unit of antitoxin or less).

*Time of occurrence of the maximum antitoxin response.* To determine the maximum antitoxin response following the third dose of toxoid, two or more tests were done on 153 patients within three months after the injection.

One hundred and forty-one patients were tested seven days after the third dose; 12 were tested within one month of the third injection. Of the 141 patients only 1 had 0.003 unit of antitoxin per cubic centimeter of serum seven days after the third injection. Thirty days later this patient's titer had increased to 0.05 unit of antitoxin. This patient received the third dose 6 months after

basic immunization. Comparative tests done on another patient who showed 0.5 unit of antitoxin on the seventh day and 0.003 unit on the fourth day, while a third patient showed 0.2 unit of antitoxin on the seventh day and 0.017 unit on the fourth day. The remaining 138 patients showed the following antitoxin levels: 0.01 unit, 1 child; 0.017 unit, 2 children; 0.05 unit, 3 children; 0.1 unit, 5 children; 0.2 unit, 20 children; 0.5 unit, 26 children; 1 unit, 27 children; 2 units, 40 children; 5 units, 11 children; 10 units, 2 children and 20 units, 1 child. These results indicated that adequate tetanus antitoxin levels were obtained seven days after the injection of a third dose of either 0.5 cc. of the combined alum-precipitated diphtheria and tetanus toxoids or the alum-precipitated tetanus toxoid alone, in 99.3 per cent of the children who were treated from 3 months to 4 years after the completion of basic immunization. For 88 of the patients the antitoxin titer was at its maximum 7 days after administration of the toxoid, while for the remaining 53 patients the titer was at its maximum within 1 month. For the former group of 88 children the maximum levels were as follows: 0.05 unit, 1 child; 0.1 unit, 2 children; 0.5 unit, 7 children; 1 unit, 17 children; from 2 to 5 units, 46 children and 10 units, 1 child. For the latter group of 53 children the maximum antitoxin levels were as follows: 0.05 unit, 1 child; 0.1 unit, 1 child; 0.5 unit, 7 children, 1 unit, 12 children; from 2 to 5 units, 29 children; 10 units, 1 child; 30 units, 1 child and 40 units, 1 child.

The 12 patients first tested within one month of receiving the third dose of toxoid showed an antitoxin level between 0.1 unit and 4 units per cubic centimeter of serum. The titer was at its maximum level on the initial test.

The foregoing observations vividly reveal the influence of a third or "booster" injection of 0.5 cc. of toxoid on the tetanus antitoxin level.

In the previous studies on comparable groups of patients who respectively received the third dose of toxoid from 3 to 15 months and from 2 to 4 years after the second dose showed that higher maximum antitoxin values were obtained after the third dose of toxoid for the majority of the children receiving the third dose from 2 to 4 years after basic immunization. In the group of children receiving the third dose within 3 to 15 months after basic immunization titers which were adequate for protection were attained by all of the children within 1 month after the "booster" dose of toxoid. However, the children given the third dose of toxoid from 2 to 4 years after the second dose attained adequate titers within 7 days. For the majority of the children who received the third dose of toxoid from 3 months to 3 years after basic immunization the antitoxin titers were at maximum level on the seventh day after the "booster" dose of toxoid was administered, while for the majority of children receiving the "booster" dose 4 years after basic immunization the antitoxin titers were at maximum levels 1 month later. For every patient the maximum was reached within 2 months or less.

*Rate of decline of the antitoxin titer from an adequate to an inadequate level.* All of the children who received a third, or "booster," dose of toxoid from 3 months to 4 years after the second injection acquired adequate tetanus antitoxin levels at least within 1 month of the third dose. In the previous studies the relation



between the percentage of children who showed a drop of antitoxin titer from an initial adequate to an inadequate level and the time required for this change was shown in the charts. For purposes of contrast, there is also shown in the charts

TABLE 1

*Maximum Tetanus Titer of Allergic Children and Titers Obtained Less Than One Year, When the Titer Dropped to 0.003 Unit of Antitoxin Per Cubic Centimeter of Blood Serum, and One Year After The Second and Third Injections of Combined Alum-Precipitated Diphtheria and Tetanus Toxoids\**

| MAXIMUM ANTITOXIN TITER  | PATIENTS |     | ANTITOXIN TITER, UNITS PER CC. OF SERUM, AFTER INJECTIONS OF TOXOID |     |          |    |       |    |      |    |     |    |     |    |     |    |           |     |
|--|----------|-----|---|-----|----------|----|-------|----|------|----|-----|----|-----|----|-----|----|-----------|-----|
|  |          |     | Less than one year 0.003†   |     | ONE YEAR |    |       |    |      |    |     |    |     |    |     |    |           |     |
|  |          |     |   |     | 0.003    |    | 0.01‡ |    | 0.05 |    | 0.1 |    | 0.2 |    | 0.5 |    | 1 or more |     |
|  | No.      | %   | No.   | %   | No.      | %  | No.   | %  | No.  | %  | No. | %  | No. | %  | No. | %  | No.       | %   |
| After second dose  |          |     |   |     |          |    |       |    |      |    |     |    |     |    |     |    |           |     |
| 0.01‡  | 11       | 8   | 8   | 73  | 3        | 27 | 0     | 0  | 0    | 0  | 0   | 0  | 0   | 0  | 0   | 0  | 0         | 0   |
| 0.05   | 19       | 14  | 10  | 53  | 4        | 21 | 4     | 21 | 1    | 5  | 0   | 0  | 0   | 0  | 0   | 0  | 0         | 5   |
| 0.1  | 21       | 15  | 7   | 33  | 4        | 19 | 6     | 29 | 4    | 19 | 0   | 0  | 0   | 0  | 0   | 0  | 0         | 10  |
| 0.2  | 45       | 32  | 5   | 11  | 5        | 11 | 27    | 60 | 6    | 14 | 1   | 2  | 1   | 2  | 0   | 0  | 0         | 35  |
| 0.5  | 23       | 16  | 1   | 4   | 1        | 4  | 9     | 39 | 8    | 35 | 2   | 9  | 2   | 9  | 0   | 0  | 0         | 21  |
| 1.0 or more  | 21       | 15  | 0   | 0   | 2        | 9  | 5     | 23 | 5    | 23 | 2   | 9  | 7   | 34 | 0   | 0  | 0         | 19  |
| Total.....   | 140      | 100 | 31  | 22  | 19       | 14 | 51    | 36 | 24   | 17 | 5   | 4  | 10  | 7  | 0   | 0  | 0         | 90  |
| After third dose given three months to four years after basic immunization |          |     |   |     |          |    |       |    |      |    |     |    |     |    |     |    |           |     |
| 0.01‡  | 1        | 1   | 1   | 100 | 0        | 0  | 0     | 0  | 0    | 0  | 0   | 0  | 0   | 0  | 0   | 0  | 0         | 0   |
| 0.1  | 3        | 2   | 1   | 33  | 0        | 0  | 2     | 67 | 0    | 0  | 0   | 0  | 0   | 0  | 0   | 0  | 0         | 2   |
| 0.2  | 10       | 7   | 0   | 0   | 2        | 20 | 6     | 60 | 1    | 10 | 1   | 10 | 0   | 0  | 0   | 0  | 0         | 8   |
| 0.5  | 26       | 19  | 0   | 0   | 0        | 0  | 9     | 35 | 7    | 27 | 10  | 38 | 0   | 0  | 0   | 0  | 0         | 26  |
| 1.0 or more  | 99       | 79  | 0   | 0   | 1        | 1  | 7     | 7  | 13   | 13 | 16  | 16 | 34  | 35 | 20  | 20 | 8         | 98  |
| Total.....   | 139      | 100 | 2   | 1   | 3        | 2  | 24    | 17 | 21   | 15 | 27  | 20 | 34  | 25 | 20  | 14 | 8         | 134 |

\* Data are included only for those children whose titrations were performed within two months after the injection of toxoid. Data for the 139 children given a third dose of toxoid between three months and four years after basic immunization and for the 140 children given two doses were obtained in previous studies (footnotes 1, 2, 3, 4 and 5) and in the original protocols. Fifty-two of the 139 children who received a third dose three months to four years after basic immunization were given tetanus alum-precipitated toxoid alone. All percentages are approximate.

† Data for patients with an antitoxin titer of 0.003 unit less than one year after the third dose are included because such titers persist at this level for at least four years.

‡ Patients with antitoxin levels 0.017 and 0.025 unit are grouped with those having a titer of 0.01 unit.

an antitoxin curve constructed from data for a comparable group of children who received only two doses of combined toxoids.

It was found that for a number of children once the antitoxin level dropped from an initial adequate to an inadequate one (0.003 unit) after the completion

of active immunization the inadequate level remained the same on subsequent tests and there was evidence to show that this level was maintained for a long period. For this reason the antitoxin titer for all these children was recorded as being inadequate up to four years after the injection of the alum-precipitated toxoids.

Examination of the charts shows that when the third, or "booster," dose of toxoid was given 3 and 4 years after basic immunization 100 per cent of the children maintained adequate immunity for a year. In contrast, of two other groups of children given the "booster" dose, 2 years and 3 to 15 months after basic immunization, maintained adequate immunity at the end of 1 year in 97 and 93 per cent of the children, respectively. The percentage of another group of children who maintained adequate immunity for a corresponding period after the second dose of toxoid was 65. It is obvious from these findings that a definitely greater percentage of children who received a third dose of toxoid had adequate immunity to tetanus 1 year later than of those given 2 doses of toxoid. Moreover, 100 per cent of two groups of children given the third, or "booster," dose 3 and 4 years after basic immunization, respectively, maintained adequate immunity for a year. This is of importance when one considers that there is no cutaneous test available for the determination of immunity to tetanus and that the titration of blood serum for tetanus antitoxin is not a practical laboratory procedure.

*Initial maximum antitoxin level compared with the levels one year and less than one year after the third dose of toxoid.* One hundred and thirty-nine children were available for retesting 1 year after receiving a third dose of toxoid. In table 1 the maximum antitoxin titer obtained within the first 2 months and the titers obtained 1 year after the administration of toxoid (or less than 1 year in those cases in which the titer dropped to the inadequate level earlier than this) are compared. The table also gives comparable data for a group of 140 children who received only 2 doses of toxoid.

The table shows that 22 per cent of the 140 children who received 2 doses of toxoid and 1 per cent of the 139 who received 3 doses showed a drop in titer from a maximum initial adequate to an inadequate level less than one year after receiving the last dose of toxoid. Only the children given 2 doses who showed a maximum initial level of 1 unit of antitoxin or more and those given 3 doses who showed a maximum initial level of 0.2 unit or more did not show a drop in titer to the inadequate level less than 1 year after the last dose of toxoid.

At the end of 1 year 14 per cent of the 140 children who received 2 doses of the toxoid, as compared with 2 per cent of the 139 who received 3 doses, showed a drop in titer to the inadequate level. Moreover, 66 per cent of the children given 3 doses as compared with only 17 per cent of the children given 2 doses had 0.1 unit of antitoxin or more per cubic centimeter of serum at the end of 1 year. This ratio of 3.9:1 is largely due to the fact that 90 per cent of the former group as compared with 31 per cent of the latter had maximum initial titers of from 0.5 to 1 unit or more of antitoxin.

Thus, it can be observed that the antitoxin titer of 36 per cent of the 140 al-

lergic children dropped from an adequate to an inadequate level one year or less than one year after the administration of 2 doses of toxoid and that only 4 per cent of the 139 allergic children given 3 doses had an inadequate titer.

Of special practical importance is the duration of adequate immunity induced by a third, or "booster," dose of tetanus toxoid in relation to the interval between the first and second doses of basic immunization and between basic immunization and the administration of the third dose. From other data and that recorded in the preceding studies it was observed that the antitoxin titer had dropped from an initial adequate to an inadequate level in 1 year or less in 7 per cent of a group of 56 children who were given the third dose of toxoid 3 to 15 months after basic immunization, in 3 per cent of a group of 30 children who were given the third injection 2 years after basic immunization and in none of the respective groups of 36 and 17 children who were given the third injection 3 and 4 years after basic immunization. Of the 140 children given 2 doses of toxoid, 108 were given 2 doses at intervals between 1 and 4 months and 32 at intervals between 5 and 10 months. The antitoxin titer dropped from an initial adequate to an inadequate level in 1 year or less in 36 per cent of the group of 108 children and in 22 per cent of the group of 32 children. Moreover, a significantly greater percentage of the latter group had responded to the highest antitoxin values not only within 3 months of receiving the 2 doses of toxoid but 1 year after the immunization.

Thus, the intervals between the third, or "booster," dose of toxoid and the completion of basic immunization and between the 2 doses comprising basic immunization had a direct influence on the antitoxin response.

*Antitoxin response to a "natural stimulus."* It was previously stated that after more than 2 months of the injection of a second or third dose of toxoid the antitoxin titers in all instances showed an appreciable decline. Also, the antitoxin titer which dropped to the inadequate level (0.003 unit per cubic centimeter of serum) after a dose of toxoid was maintained at this residual level for at least 4 years. Nevertheless, retests on a number of these children were carried out in order to detect any sharp rise of antitoxin titer which might possibly follow a "natural stimulus." In this connection it was revealed from a study of the records of the 1549 tests done after the second and third injections that titers of all except 2 children fell progressively from the initial maximum levels. For 1 child the maximum initial titer was 0.2 unit of antitoxin 7 days after the third dose was given. Eight months later the titer dropped to 0.017 unit of antitoxin; one year later it rose to 0.1 unit (and the same value was obtained on rechecking the serum) and 2 years later the titer dropped to and was maintained at 0.017 unit for another one and one-half years. For the other child the maximum initial titer was 0.05 unit of antitoxin 1 month after the second dose of combined toxoids was given and 6 months later the titer was the same. Ten months later the titer rose to 0.1 unit of antitoxin and 1 year later it was 0.2 unit. From two to three and one-half years after the second dose the titer was maintained at the antitoxin level of 0.05 unit which dropped 4 years later to 0.017 unit. It is extremely difficult to explain these results satisfactorily on the basis of possible

technical error, a plausible argument when applied to minor changes in titer (as observed in 14 children with residual titers of 0.01 unit of antitoxin) but not to respective increases in titer of 6 and 4 times greater than the control. The idea that these increases in titer may have followed a natural stimulus cannot be discarded. However, if this increase in titer should be so regarded then retests repeated over a period of five years on actively immunized children known to maintain residual titers of from 0.003 to 0.017 unit of antitoxin or higher, indicates that a rise in tetanus antitoxin values following a natural stimulus in actively immunized children is an uncommon occurrence. In view of the above findings the idea that a tetanus antitoxin response may follow a natural exposure in an actively immunized person cannot at the moment be seriously entertained. Moreover, a natural immunity in a nonimmunized person following exposure to tetanus spores has yet to be proved.

*Reactions and sensitivity.* A concentration of antigens or other substances contained in a given volume of a preparation intended for subcutaneous injection probably bears a closer causal relation to a local reaction in a person insensitive to a specific substance than any other factor. It may be expected that in a majority of instances injection of 0.5 cc. of toxoid will be followed by few and milder reactions than injections of 1 cc. of a corresponding preparation. Moreover, the tetanus antitoxin values following injection of 0.5 cc. of combined alum-precipitated diphtheria and tetanus toxoids or alum-precipitated tetanus toxoid alone, compares favorably with the titers obtained after a 1 cc. dose of the corresponding toxoid. In children the need for using the smaller volume of the toxoid preparations such as was employed in this study, is obvious.

For the first 98 of the 159 children in this study the third, or "booster," dose consisted of combined alum-precipitated diphtheria and tetanus toxoids. Thirty-six of these 98 children had local reactions. Eleven of these 36 children, of whom 7 had severe local reactions and 1 a moderate and 3 a mild reaction, some hours after the injection of the combined toxoids experienced elevations of temperature ranging up to 104°F., which lasted from 1 to 2 days. The incidence of febrile reactions in this group of 98 children, 11 per cent, contrasts with 1 per cent in the group of 186 children given only 2 doses of combined toxoids. When the 11 per cent of febrile reactions is analyzed in relation to the interval between basic immunization and the administration of the "booster" dose it is found that the longer the interval between the second and third doses of combined toxoids the incidence of febrile reaction became progressively higher. The incidence of febrile reactions in the group of children given combined toxoids 3 to 15 months after basic immunization, 3 per cent, contrasts with 22 per cent in the group of children given combined toxoids 2 years after basic immunization and with 33 per cent in the group of children given combined toxoids three years after basic immunization.

The remaining 61 of the 159 allergic children comprising this study were given a "booster" dose of only alum-precipitated tetanus toxoid. Not 1 of these children showed a febrile or general allergic reaction after the injection of toxoid. However, 5 children experienced a moderate and 6 a severe local reaction. There

were two general allergic reactions (urticaria and allergic rhinitis) encountered in the active immunization of 186 allergic children who have had two to five doses of combined toxoids, including 61 children who have had a third dose of alum-precipitated tetanus toxoid alone, that is, in a total of 534 injections (an incidence of 0.37 per cent).

The scratch tests, performed with undiluted combined alum-precipitated diphtheria and tetanus toxoids and with tetanus alum-precipitated toxoid alone, did not produce positive reactions, immediate or delayed, in any of the children observed in this study. In view of these negative reactions to cutaneous tests with toxoid preparations, the systemic reactions (elevation of temperature, allergic rhinitis and urticaria) after the administration of the combined alum-precipitated diphtheria and tetanus toxoids can be attributed to the increased sensitivity to the protein of the diphtheria bacillus rather than to the proteose or other substance in the toxoid preparation. The probability of induced sensitivity to tetanus bacillus protein is remote.

In view of the above findings and in order to avoid the accident of a febrile or systemic allergic reaction following a "booster" dose of combined alum-precipitated diphtheria and tetanus toxoids it is advisable to employ alum-precipitated tetanus toxoid only, especially when the "booster" dose is given to older children 2 or more years after the completion of basic immunization with 2 doses of the combined toxoids.

Local and general reactions following the subcutaneous injection of the combined toxoids were fully discussed in a previous communication (1).

#### COMMENT

Bacteria are the most complex antigens in common use, and their antigenic structure is closely related to virulence and to all bacterial substances. Toxin is one of the products of bacteria to which an antigenic response may be provoked. The best and most durable immunity is that actively acquired in which the body cells are stimulated and trained, as it were, to build up an effective defense against the offensive forces of an invading pathogenic substance. Thus, one of the most fundamental concepts of the role of allergy in bacterial immunization is the fact that once the cells of the body have come in contact with an antigenic substance they never again fear their original relation to that substance. Long after antibody production has ceased the cells remain in such a condition that contact with the antigen will stimulate them to produce antibodies more quickly and more abundantly than usual. Within certain limits, repeated injections are, on this account, more effective in raising the antibody titer to a higher level than a single injection even of a large dose.

A natural immunity to certain diseases is acquired through invasion by the pathogenic organism specific for the disease, and the advantages persist after recovery from the disease. Since a natural immunity or a "natural stimulus" in a person actively immunized against tetanus has not been demonstrated, the importance of the role of the two basic injections of toxoid and the third, or "booster," dose in the establishment of an effectual immunity against tetanus,



cannot be overemphasized. The capacity to respond to more effective and higher antitoxin values to a third dose of toxoid as compared to the two basic injections, and so insuring protection of the patient from tetanus, is evidenced by the results obtained with the 159 allergic children comprising this study.

In the absence of any practical test to determine immunity to tetanus, treatment with alum-precipitated tetanus toxoid must be depended on to induce adequate immunity in almost all, if not all, persons treated. Two doses effected immunity in 176, or 94.6 per cent, of 186 children, while the remainder acquired adequate protection after a third dose. Hence, from a clinical viewpoint it appears that to produce adequate immunity to tetanus in children of all ages three doses of 0.5 cc. each of alum-precipitated toxoid (of a capacity of 30,000 minimum lethal doses per cubic centimeter) should be administered at intervals of 1 month or more. However, the results reported in the four preceding studies reveal that the intervals (up to 4 years) between the two basic doses of the toxoid and between these and the third dose have a direct influence on the antitoxin response. The longer the intervals (up to three years) between the injections of the toxoid the higher the antitoxin response. The group of children given the third and second doses of toxoid at intervals of 3 to 15 months responded with the lowest antitoxin values.

#### SUMMARY AND CONCLUSIONS

Three months to 4 years after the completion of basic immunization with two 0.5 cc. doses of combined alum-precipitated diphtheria and tetanus toxoids, 159 allergic children were given a third, or "booster," dose of 0.5 cc. (98 children received combined alum-precipitated toxoids and 61 children alum-precipitated tetanus toxoid alone). The level of antitoxin was determined at various intervals after the second and after the third doses of the toxoids, and the respective totals of 747 and 800 specimens of blood serum were titrated for tetanus antitoxin.

An elevation of temperature which lasted from 1 to 2 days followed the administration of the third dose of combined toxoids in 11 per cent of the children. This incidence of febrile reactions contrasts with 1 per cent in the group of children given only the two basic doses of combined toxoids. It was found that the longer the interval between the second and third doses of combined toxoids the incidence of febrile reaction becomes progressively higher (from 3 to 33 per cent in the respective groups of children given combined toxoids at intervals of 3 to 15 months and 3 years after basic immunization).

Two systemic allergic reactions (urticaria and allergic rhinitis) were encountered in the active immunization of 186 allergic children who have had 2 or more doses of combined toxoids or tetanus toxoid alone, that is, in a total of 534 injections (an incidence of 0.37 per cent).

No allergic or febrile reactions were encountered in the children given alum-precipitated tetanus toxoid alone.

Scratch tests with the undiluted toxoid preparations were negative.

The intervals between the two basic doses of the combined toxoids and between these and the third, or "booster," dose have a direct influence on the antitoxin

response. The longer the intervals (up to 3 years) between the injections of toxoid the higher the antitoxin response.

A third dose of combined toxoids or tetanus toxoid alone, given to allergic children between 3 months and 4 years after the completion of basic immunization with 2 doses of combined toxoids was followed within 1 month in all instances by an adequate tetanus antitoxin titer which was always higher and lasted for a much longer period than that which followed basic immunization. (After basic immunization adequate immunity was attained by only 94.6 per cent of the children). The antitoxin titer obtained on the seventh day after the third injection was adequate in 99.6 per cent of the children and was at its maximum in the majority of instances. The 1 case (0.4 per cent) with inadequate antitoxin titer after the third dose of toxoid attained an adequate and maximum antitoxin titer on the seventh day after the fourth dose.

Finally, when a child has had basic immunization with 2 doses of combined alum-precipitated diphtheria and tetanus toxoids and a third, or "booster," injection of toxoid is administered two to four years later, then alum-precipitated tetanus toxoid alone should be used in order to keep local and systemic allergic reactions at the minimum level.

#### REFERENCES

1. PESHKIN, M. M.: Immunity to tetanus induced by combined alum-precipitated diphtheria and tetanus toxoids; based on a study of one hundred and eighty-six allergic children, *Am. J. Dis. Child.*, 62: 9, 1941.
2. PESHKIN, M. M.: Immunity to tetanus induced by combined alum-precipitated diphtheria and tetanus toxoids; based on a study of sixty-five allergic children given a third or "repeat" dose, *Am. J. Dis. Child.*, 62: 309, 1941.
3. PESHKIN, M. M.: Immunity to tetanus induced by a third dose of toxoid two years after basic immunization; based on a study of thirty-one allergic children, *Am. J. Dis. Child.*, 65: 873, 1943.
4. PESHKIN, M. M.: Immunity to tetanus induced by a third dose of toxoid three years after basic immunization; based on a study of thirty-eight allergic children, *Am. J. Dis. Child.* 67: 22, 1944.
5. PESHKIN, M. M.: Immunity to Tetanus Induced by a Third Dose of Toxoid Four Years After Basic Immunization, based on a Study of Twenty-Five Allergic Children (to be published).
6. GOLD, H.: Studies in tetanus toxoid. I. Active immunization of allergic individuals with tetanus toxoid, alum-precipitated, refined, *J. Allergy*, 8: 230, 1937. On the value of a "repeat" injection of tetanus toxoid (secondary stimulus) in active immunization against tetanus, *J. Lab. & Clin. Med.*, 25: 506, 1940.
7. JONES, F. G., cited by Peshkin (1); RAMON, G.; cited by Gold (5); RAMON, G., Combined (active-passive) prophylaxis and treatment of diphtheria or tetanus, *J. A. M. A.*, 114: 2366, 1940.
8. SNEATH, P. A. T., KERSLAKE, E. G., AND SCRUBY, F.: Tetanus immunity: resistance of guinea pig to lethal spore doses induced by active and passive immunization, *Am. J. Hyg.*, 25: 464, 1937.

# DERMOID CYST OF OVARY CONTAINING A STRUCTURE SIMILAR TO A HUMAN BODY (HOMUNCULUS)

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Description of malformations and monstrosities has been a primitive form of pathology, just as the chronicling of unusual happenings antedated the science of the historian. Up to this day we have peculiar feelings, difficult to analyze, when we look at a monstrosity even if we do not believe any more that the mother must have had intercourse with the devil. The deeply rooted consciousness of our ego as a unit, psychic and physical, is shocked by the aspect of something that mimics the individual without attaining the cherished accustomed "gestalt" of the human body. The amount of interest pathologists have taken in malformations has fluctuated, the changes being in part explained by the prevailing trends in oncology and embryology. The time seems ripe for renewed interest in malformations, with new lines of approach available. This thought, and the lack of a similar report in modern American literature have caused the writing of this paper.

*History:* (by Dr. Harry Cohen). The patient was a 22 year old healthy woman, married for three and a half years. She had one child, 14 months old. She had been sick with puerperal fever for two months. No other illnesses were reported. There were no abdominal symptoms, but a large hard mass could be palpated vaginally, filling the cul-de-sac and pressing upon the right fornix. The preoperative diagnosis was dermoid cyst of right ovary. At operation a mass, the size of a cantaloupe, was found firmly adherent to pelvic structures and to intestine. It was freed by blunt dissection and removed intact. The patient was discharged six days after operation. Her further course was uneventful.

## GROSS OBSERVATIONS

The specimen looks like a dermoid cyst (11 x 8 x 6 cm.) with a 7 cm. long line of attachment. The lumen is filled with an unattached round solid mass whose outer layers consist of tallow and intertwined hairs which can be removed easily. The remaining firm central mass is irregularly ovoid (6.5 x 5.5 x 4.5 cm.). Its surface is very pale, skin-like, with only a few scattered, firmly attached hairs. Viewed from one side (fig. 2), the specimen looks like disproportionally large round buttocks with two rudimentary lower extremities and a tail on top in midline. A central depression would correspond to a coccygeal groove; it contains a small, ovoid, soft protrusion. Hard masses can be moved against each other in the lower extremities. No toes or nails are noted. On turning the specimen around (fig. 1) one sees a fin-like right upper extremity with a bunch of hairs under it. No left upper extremity can be recognized, an indistinct swelling occupies its place. A round filamentous structure, 1.2 cm. long, hangs down in midline, slightly below the level of the upper extremity. Its end tapers and looks torn. There are no external genital organs and no anal opening. On the pole opposite the lower extremities the specimen is hard, with little soft tissue between the skin and a large, round, very hard, skull-like central mass. The surface here is broken by grooves and wrinkles. Two pigmented dots are located where one would expect the eyes, and a small deep funnel from which a mustard seed sized nodule protrudes is situated in the place of nose or mouth (fig. 3). On Roentgen ray examination (Dr. A. J. Bendick) a rudimentary skeletal system is seen in which a head, thorax, pelvis and extremities can be outlined. The structure is that of adult bone.

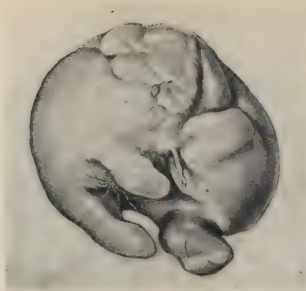


FIG. 1



FIG. 2

FIG. 1. Homunculus (little man) from inside of ovarian dermoid cyst. Two stunted lower extremities, fin-like right upper extremity with a bunch of hair under it. Torn umbilical cord. Naked skin with single hairs. (Drawing, natural size.)

FIG. 2. Rear-view. Fat "buttocks," coccygeal groove with ovoid protrusion, tail. (Drawing, natural size.)

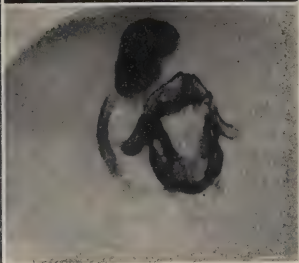
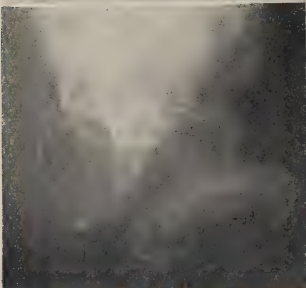
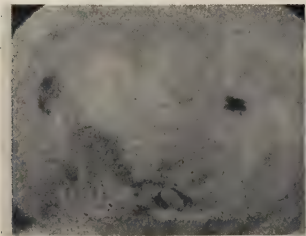


FIG. 3. (Upper left) Two pigmented dots in place of eyes. Indefinite structures in the region of nose or mouth. (From kodachrome.)

FIG. 5. (Upper right) Foreshortened side-view. Vertebrae, outline of large foot.

FIG. 6. (Lower left) Contours of foot. (Enlarged from fig. 5.)

FIG. 7. (Lower right) Vertebra, rib.

The specimen, after thorough fixation, is cut into six slices, the lowermost one containing the legs. The skull bone is ivory-like, exceedingly hard. It contains a cavity, 7 mm. diameter, which is filled with pale pinkish-brown, soft, homogeneous matter. A thin membrane lines the cavity. A thin bony shell, also 7 mm. diameter, adjoins the skull-like portion. The skin of the "face" overlies the bone almost directly. Otherwise a thick layer of fat is interposed between skin and skeleton. There is no trace of inner organs or of muscle.

In the roughly antero-posterior x-ray picture (fig. 4) the center is occupied by a pelvis-like structure, which seems to be of one piece. Hip joints cannot be recognized. It would be hazardous to interpret the subdivisions of the lower extremities, except for the distinct delicate outlines of a foot (fig. 6). Spinal column is represented by three or four vertebrae.



FIG. 4. Antero-posterior Roentgen picture. Large dense bone in place of head. Structures suggesting shoulder girdle and upper extremities, pelvis, lower extremities.

Three intervertebral foramina can be recognized (fig. 5). In one of the slices (fig. 7) a vertebra with body, transverse processes and posterior arch is in focus. The spinous process is missing. On the rib, in the same picture, the torsion is characteristic. Thorax and shoulder girdle cannot be made out in the snarled shadows above the pelvis. It is doubtful how far the laterally protruding shadows belong to upper extremities. The heavy shadow of the "skull" reveals no detail. In another picture (not reproduced here) the central cavity was recognizable.

#### NOMENCLATURE

It is not easy to find a name for such a structure. Names that prejudice anything concerning the unknown nature and origin should be avoided. To



call the specimen "fetiform," for instance, is not advisable; it is part of a dermoid cyst, and consists of mature adult tissue. Many authors have apologized for using the word "fetiform."<sup>1</sup> A small human within another human will naturally suggest the idea of a fetus. The terms "mannikin" and "Zwergmensch" (dwarf man) are good, but are not internationally understood. The latin word "homunculus" seems preferable. Literally meaning "a small human," it was used by Paracelsus and Goethe to designate a human being not produced by procreation. I do not know who introduced it into modern medical nomenclature. John Miller (1937) uses it in connection with a case of J. K. Thornton (1882).

#### MICROSCOPIC OBSERVATIONS

Fifteen different portions of the cyst wall are examined. In all of them three layers can be seen more or less distinctly. The inner layer consists of loose tissue with many lymphocytes and plasmacells. There are very numerous, irregularly distributed, small empty spaces, surrounded by foreign body giant cells. Many of them contain a hair shaft. No cellular elements of hairs are found. There is no lining epithelium or endothelium in any of the sections. The intermediate layer is formed essentially by connective tissue with few nuclei while in the outer layer spindle-shaped nuclei are abundant. In some of the sections the middle and outer layers contain primordial follicles, follicular cysts and an occasional corpus atreticum. No true corpora fibrosa are found. In all the sections the tissues of the cyst wall are well-preserved, with perfect nuclear staining.

In contrast, all sections taken from the homunculus appear practically necrotic, except for bone and cartilage. As seen in the gross specimen, fat tissue occupies most of the space. It is of adult type, as all the other tissues are. The squamous epithelium of the skin can be recognized in places; there are sebaceous glands, sweat glands, hairs. In the region of the mouth, muscle and glandular structures can be recognized. Corresponding to the black dots, in the place of the eyes, characteristic melanophores are seen but there are no typical eye structures. The pigment gives the microchemical reactions of melanin. Thick elastic lamellae, in the wall of blood vessels, for instance, take the Weigert stain while the delicate fibers in the corpus papillare of the skin cannot be demonstrated. The section marked brain contains a characteristic ganglion with large ganglion cells and thick bundles of nerves. The staining in this section also is very indistinct. In a cross section from the tail slight calcification is noted. No further details can be recognized. There is no trace of other inner organs.

The best preserved tissue, the bone, also is of mature type throughout. Dr. Henry L. Jaffe, who was kind enough to study the slides, felt that some of the structures might well represent joints, others cartilaginous ends of ribs.

The inflammation in the cyst wall is the only microscopic finding that calls for a clinical interpretation. It may have been caused by the hairs, or it may be a remnant of the puerperal infection.

#### COMMENT

Modern American medical literature contains little about such cases. They are very rare. These specimens are so striking, almost exciting, that probably most observations have been published.

<sup>1</sup> The term "fetal inclusion" is commonly used to designate man-like structures found inside the body, mostly in the abdomen but not in the ovary. In this context the word "fetal" can be accepted as indicating the time of origin, namely fetal life, but not as indicating any similarity with a fetus. The name "inclusion" seems fitting even if the theoretical considerations that led to its introduction do not hold any more today.

In the November meeting (1902) of the New York Obstetrical Society, Hiram N. Vineberg demonstrated a dermoid cyst from a 30 year old Para III. A solid body, the size of a turkey's egg, was attached to the inside of the cyst. It bore the shape of the trunk of a human fetus. On either side at its inferior part was a rudimentary leg with five rudimentary toes. In the center was a penis-like projection.

Shortly afterwards, in the February meeting, 1904, J. Riddle Goffe gave the following description of what he had found in an ovarian dermoid of a young girl. "... six inches long... general appearance and contour of a human monstrosity... something like a hydrocephalic head attached at the shoulders... two buds in place of the upper extremities; the trunk resembled in contour closely that of a child, but at the seat of the coccyx a tail projected. The object terminated in... two fused legs with one big toe and a nail." Unfortunately, there are no pictures and no records of more detailed examination of both specimens.

A comprehensive study of the subject was made by Robert Meyer in 1924. He described two cases of his own, he re-examined three specimens previously reported by others (Köhler, Albrecht, Staffel-Burghardt), and discussed the cases of Key, Répin, Shattock, Wertheim, Rosenstein, Askanazy, Ingier, Heijl and Kaboth. Interested readers are referred to this important, detailed, well-illustrated paper. The title of Robert Meyer's paper "Teratomata (Dermoid-Cystomata) of ovary with free pelvic end and with extremities," stresses the most important feature all these cases have in common. In the thickening on the inside of ordinary dermoid cysts, the so-called dermoid plug, components of the upper portion of the body are represented as teeth, brain, respiratory tract, thyroid. Organs of the lower part of the body are seldom found. The homunculi to the contrary, are conspicuous by lower extremities, pelvis, external genitals. Aschoff very aptly talks about "Kaudalhöcker" (caudal hump) in contrast to the usual "Kopfhöcker" (cephalic hump) of the ordinary dermoid cyst. Needless to say, there are no sharp distinctions, and intermediate forms are abundant. A dermoid cyst may contain a single finger (or toe), a more or less distinct skull, a structure looking like external genitals or a breast, etc. Even if we restrict our considerations to the definite homunculi there remains much variety, and not one of the cases reported in the literature is entirely like the one reported here. Its unique feature is the free position in the dermoid cavity, or, what is more significant, its previous attachment by the umbilical cord only. An umbilical cord, or its remnants, has been found in several instances, but invariably there was another broad attachment of the homunculus to the cyst wall. Robert Meyer (page 749) in 1924, wrote "so far a case is lacking in which the imitation of a human body reaches such a degree that the whole body, attached by means of the cord, hangs free in the cyst cavity." My case fills this gap.

The specimen, in my opinion, admits of no other explanation than that of a previous attachment by means of the cord alone, with later severing of the cord, probably by twisting. The unbroken round contours of the homunculus which

give him the aspect of a crudely made doll, preclude the idea of another previous continuity with the cyst wall, while the umbilical cord by its very nature must have been attached. And the compact round homunculus, hanging by a thin cord into a fluid of low density, could easily rotate  $360^\circ$  or more, shut off the blood stream in the cord, and finally twist the cord off. The necrosis of the tissues indicates that this has taken place some time ago. Cases have been described (Gentili, Haffter, Krömer, Neck and Nauwerck) in which an ordinary dermoid plug did not have a broad base, as usually, but was attached by means of a thin short stalk; in one instance (Krömer) the stalk was somewhat twisted. I do not know of any large or small corpus liberum in a dermoid cyst which might be a twisted off homunculus or dermoid plug. If our patient had carried the dermoid with the twisted off homunculus into old age a large free "stone" inside a cyst might have resulted.

While, as mentioned, no homunculus in a dermoid cyst has been reported with attachment by the cord only, there is on record a closely related structure, namely a peritoneal fetal inclusion, which was attached by the cord only. (fig. 15). The specimen was removed from the abdominal cavity of a newborn after death, and given to E. Klebs. The cyst was situated behind the mesocolon transversum. The "umbilical artery" came from the aorta of the host. Klebs considered this specimen unique in 1876, and it may still be so.

Reproduction of a few pictures from the literature will help us in emphasizing some of the outstanding features. The skeleton shown in Figure 8 (Répin) demonstrates the predominance of lower extremities over the upper ones and of distal portions over proximal ones. The skull bones are very thick, there is no neck. The three protrusions on top of the head are teeth. The whole structure, of which only the dissected out skeleton is shown, was attached with its back to the cyst wall, the head portion touching the ovary. The skin was thick and hairy; it was continuous with the lining of the cyst. A 3 mm. long protrusion in the pubic region had an opening at its tip and was surrounded by hairs. It was grossly interpreted as penis but turned out to be breast gland, microscopically. There were two microscopically normal sciatic nerves. This dermoid cyst was first noted by the patient at the age of 31 years, before marriage.

In Figure 9 (case Albrecht, from Robert Meyer) there is no head and only one very small upper extremity. Again, the disproportionally large feet are conspicuous and a round swelling in the knee region. This homunculus had much pubic hair. The ovarian cyst had been removed from an 18 year old normal girl.

Fig. 10 is reproduced from a water color in Askanazy's paper (1905). The dermoid cyst came from a 35 year old married nulligravida. The patient had peritoneal carcinosis, primary seat unknown; no autopsy. There is a large vesicular "head" with a large pigmented eye spot, and long tufts of hair. The small protrusions on the head contain cartilage. The trunk is without detail. Between the sprawling legs a hairy pubic region with labia and an opening is conspicuous. The opening could be probed for a distance of 7 mm. Microscopically, characteristic corpora cavernosa were found. In the x-ray picture



FIG 8

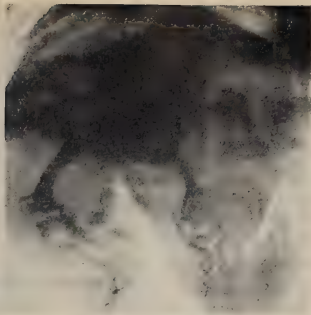


FIG. 9

FIG. 8. Skeleton from dermoid cyst. (Charles Répin, Thèse de Paris, 1892.) Natural size.

FIG. 9. Two lower extremities, one upper extremity (fig. 7, case Albrecht; Robert Meyer: Arch. f. Gyn., vol. 123, 1925).

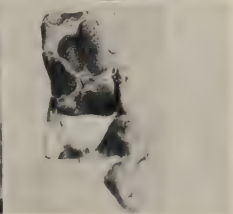
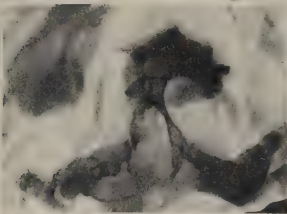
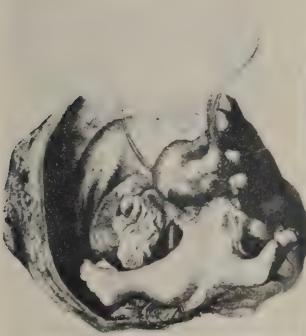


FIG. 10. (Upper left) Large soft head with long blonde hair and pigmented eye dot. Vulva with opening and labia surrounded by coarse dark hair. Trunk, lower extremities (fig. 2, Askanazy, Bibliotheca Medica, C, 19, 1905).

FIG. 11. (Lower left) Two lower extremities, in sprawling position, indistinct pelvic shadow (fig. 3, Askanazy, Bibliotheca Medica, C, 19, 1905).

FIG. 12. (Upper right) Projection into dermoid cyst, 6 cm. long. Skeletal parts, side-view. (S. G. Shattock, Transact. Path. Soc. London, 58: 267, 1907, fig. 3.)

FIG. 13. (Lower right) Same; antero-posterior view of skeleton.

of the foregoing (fig. 11) the two misshapen, widely abducted legs are shown, again with a giant foot.

In Figures 12 and 13 (Shattock 1907) pubic bones and major trochanters approach the normal shape, the bony structures above and below are quite irregular. There were thick layers of fat tissue. There was a vulva with long hairs, the skin otherwise was hairless. From a foramen a well-defined spinal cord was pulled out; its nerve fibres were medullated.

The freak skeleton of Figure 14 (Kaboth 1924) repeats the characteristic features: large distal portions of lower extremities, marked pelvic structures, obviously an os sacrum with promontory, and very heavy skull bones. The

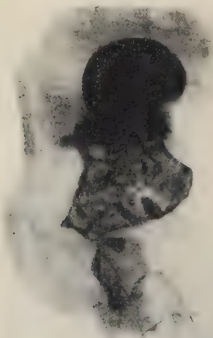


FIG. 14

FIG. 14. Skull, vertebrae, sacrum, lower extremities (distal parts retouched). (Georg Kaboth, Arch. f. Gyn. 122, 1924.)



FIG. 15

FIG. 15. From abdominal cavity of newborn. Note the umbilical cord, with an artery (a'') coming from the aorta of the host (a'). Natural size. (E. Klebs: Handbuch d. Pathol. Anat., 1: 2, 1013, 1876.)

segmentation of the spine is well seen. The whole, 10 cm. long, structure was attached to the cyst wall by the neck. An umbilical cord, 5 cm. long, connected it with an enterocystoma. The vulva was well-developed, its opening led into a canal. Except for the pelvis, the trunk consisted only of skin, fat, connective tissue and bone, as in my specimen.

Unfortunately, a number of pertaining cases have been reported very briefly and without pictures. One beautiful specimen is entirely lost. In 1833 Cruveilhier said in the Société Anatomique that, a few years previously, the society had received an ovarian cyst containing a complete skeleton, the size of a bee. (Quoted from Répin). In his atlas Cruveilhier gives a picture of a skeletal mass



in another dermoid cyst, together with an almost overcautious description. Hence his expression "a complete skeleton" has to be taken seriously.

Even this cursory survey indicates that the madness of these malformations is not entirely without method. The repeated occurrence of certain features is beyond the limit of probability: the thick skull bones, the accent on pelvis and external genitals, the differentiation of distal portions, the smallness or absence of upper extremities, the paucity of inner organs in comparison with skin, fat tissue and skeleton, the absence of skeletal muscle in the presence of the corresponding bones, and nerves. In an attempt to explain such observations we turn to the theories concerning the genesis of teratomatous structures in general and especially of ovarian dermoids. There is the widely accepted blastomere theory (Marchand-Bonnet) which assumes that early in embryonic life one cell was displaced, and developed, so to say, on its own account. There is the older theory of parthenogenesis which has received new vigor through the finding of early developmental phases in the ovary of virginal guinea pigs, (L. Loeb, Courrier and Oberling). There still is, finally, the theory of the fertilized polar body. I shall not revive the discussion of the merits and shortcomings of the divergent views which, as Ewing wrote in 1940, "are almost as divergent as ever." For the blastomere theory it is difficult to explain the seat in the ovary; the theory of parthenogenesis has difficulties in explaining other localizations (see Ewing 1940, p. 682, ff.). The peculiar predominance of certain body parts and organs in the ordinary dermoid and of others in the homunculus clamors for an explanation that transcends mere anatomical and spatial disturbances. Such explanations may be made possible by applying Spemann's organizer theory of embryonic development to teratology. An organizer is a tissue structure—or a substance elaborated by tissue—which induces surrounding tissues to develop in a certain way. The process is called induction. The ultimate fate of an embryonic tissue is not predetermined. A tissue which, in the course of normal development, would form one organ can be exchanged by grafting against tissue which would form another organ, without disturbing the development of the embryo. That means the existence of determining influences which are stronger than the inherent character of the cells. The seats of these influences are called induction centers. The strongest induction center is the dorsal lip of the blastopore. A fragment of this tissue, when transplanted to another part of the embryo, will induce the development of an almost complete second embryo. This experimental result will automatically call to mind the "fetal inclusion," and not much imagination is required to draw parallels between known teratomatous structures and variable spatial and temporal irregularities of organizer action. The time factor should be borne in mind.<sup>2</sup> Organizer action of normal character and localization might

<sup>2</sup> In one common malformation the time factor is evident. The suprarenal glands of most anencephali are very small and their structure, in some respects, corresponds to that of a 2 year old infant. As Marchand (*l. c.* p. 727) said long ago, there are abnormalities of development in time which are not necessarily associated with morphological malformation. He gives precocious puberty as an example (see Novak).

result in malformation if it is delayed or premature. One set of organizers might lead to the ordinary dermoid plug with cephalic predominance, a little change in organizer set-up might favor thyroid growth and result in an ovarian sturma, and still another, rarely occurring, arrangement of induction agents will yield a homunculus.

In most of the American, British, French and German pathology textbooks and monographs consulted, Spemann's organizer theory is not mentioned. Theoretical science, sometimes, progresses rapidly but it spreads slowly. Ewing (1940) in the chapter on teratoma refers to organizers and induction. He stresses the growing recognition that the germ layers are not specific and that originally simple embryonal tissues may be a source of complex teratomata. In the chapter on ovarian tumors Ewing does not mention organizers. The topic is discussed in some detail by Gruber in the chapter on malformations in Aschoff's textbook (1936). In the chapter on ovarian dermoids, written by Aschoff himself, organizers are not mentioned.

In the special literature on malformations, fetal inclusions, teratomata and dermoids, Budde (1926) was the first to draw on organizers and induction for explanation. He quotes prophetic utterances made by Meckel and Oskar Hertwig. Budde's article has received little attention.

G. W. Nicholson, who has devoted numerous papers to a highly critical analysis of teratomata, feels that whoever is acquainted with Spemann's experiments will not maintain for one moment that adult teratoma arises in dislocated blastomeres (1934). Thus Nicholson wants to replace the static anatomical theories entirely by a dynamic functional concept. As Joseph Needham said, in his lecture on chemistry and biology of organized growth, more people must have realized that organizer phenomena provide the basis for a modern theory of the origin of teratomata. Krafka in 1936 has drawn a diagrammatic chart to show the parallelism between diffusion of organizers in the embryo and the distribution of teratomata.

S. E. Moolten (1942) has applied Spemann's ideas to problems of special pathology. Moolten considers the possibility that many malformations are caused by some interruption in organizer function.

In my opinion, one should not discard the older theories entirely in favor of the organizer idea. An ovarian dermoid might very well have originated in a sex cell, but its final shape, its composition of organs, body parts and tissues might have been determined by organizers. With more advanced knowledge of the chemical nature of organizers parts of the problem might be accessible to experiment. Organizers of known action might be studied in their influence upon the artificial production of teratoma, by Michalowsky's technique, for instance. Michalowsky has produced teratoma in the testicles of roosters by injecting strong inorganic irritants. Will it be possible to influence the composition of such a teratoma by applying known organizer substances to the testicle in different phases of the experiment?

The absence of gonadal structures and sex cells has been a pivotal point in the discussion about the nature of ovarian dermoids, of teratomata and fetal

inclusions. I am not entirely sure of the prime importance of this point. Fetal inclusions and even some *holoacardii amorphi* resemble the homunculi to a high degree. Shall we consider them entirely different because they may contain a sex gland? Other organs also, liver for instance, have hardly ever been found with certainty in ovarian dermoids. Many more homunculi and similar structures should be examined, with serial sectioning of the regions concerned, before we can be fully convinced that they never contain gonadal structures. This point is important because presence or absence of a sex gland is a much used criterion for considering a formation as an individual by itself or not. The validity of these distinctions has to be proven.

Looking at the x-ray pictures of Kaboth's case and of the one described here, one wonders about the critical attitude of some authors who refuse to accept such structures as something comparable to a human organism. Nicholson (vol. 84, p. 417), who gives a detailed description of Kaboth's case, rejects the homology of a bony structure in a teratoma with a somatic bone by saying: "A bone is that bone and no other because of its life history, location and function in the body, much more than because of its shape." When I find a bone, as pictured in Figure 7, lying somewhere in the sand, I call it a vertebra. Should it be denied this interpretation when found in connection with similar bones in the body axis of a teratomatous structure? And, to go from the detail to the whole, I still feel that we have a right to compare the homunculus to an incomplete human being. Its development—which nobody has observed—must necessarily have been a caricature of embryonic processes. Even if, as Nicholson states, a "germ" much simpler than a parthenogenetic ovum or an early blastomere was the source of the teratomatous structure, its development, perhaps influenced by abnormal induction, was abnormal embryogenesis. The experimental embryologists themselves talk about "a second embryo" induced by the grafting of blastopore-lip tissue.

Needham, in a similar vein, writes that no teratoma has ever been found to show signs of axiation or metameric segmentation. I refer the reader again to Figures 5 and 14.

At the beginning of this paper it has been said that teratology is influenced by embryology and oncology. As long as Cohnheim's theory was dominating, tumors and malformations were closely allied subjects. With the progress of experimental cancer research the irritation theory got the upper hand, developmental defects were considered less important in the genesis of tumors, and a gap opened between oncology and teratology. The similarities in the action of organizers, hormones and carcinogens are apt to bridge this gap, promising a coming unified aspect of previously heterogenous appearing phenomena.

#### SUMMARY

1. A dermoid cyst is described containing, free in the lumen, a miniature human-like structure (homunculus) with remnants of an umbilical cord.

2. Pertaining literature and theories are discussed with emphasis on the organizer theory.

BIBLIOGRAPHY<sup>3</sup>

- ASCHOFF, L.: *Pathologische Anatomie*, ed. 8, 1936, vol. 2.
- ASKANAZY, M.: Die Dermoidcysten des Eierstocks. *Bibl. Med.*, Abt. C., Heft 19, Stuttgart, 1905.
- BUDDE, MAX: Über die Genese der Fetalinkclusionen. *Beitr. z. path. Anat. (Ziegler's)*, 75: 357, 1926.
- COURRIER, R., AND OBERLING: Parthénogénèse spontanée dans l'ovaire du cobaye. *Bull. Soc. anat. de Paris*, 1923.
- CRUVEILHIER, J.: *Anat. Path.*, 1: 18, 1829.
- EWING, JAMES: *Neoplastic Diseases*, ed. 4, 1940, p. 1041.
- GOFFE, J. RIDDLE: *Am. J. Obst.*, 49: 675, 1904. (New York Obstetrical Society, 1904.)
- GRUBER, G. B.: In *Aschoff's Pathologische Anatomie*, 1936, vol. 1.
- INGIER, ALEXANDRA: Beiträge zur Kasuistik und Genese der Ovarialdermoide. *Beitr. z. path. Anat. (Ziegler's)*, 43: 356, 1908.
- KABOTH, GEORG: Über die Morphologie und Genese foetusartiger Ovarialteratome (Dermoide). *Archiv für Gynaekologie*, 122: 803, 1924.
- KLEBS, E.: *Handbuch der Pathologischen Anatomie*, 1: 1013, part 2, 1876.
- KRAFKA, JOSEPH JR.: Teratoma, An explanation of its cause based on the organizer theory of embryology. *Arch. Path.* 21: 756, 1936.
- LOEB, LEO: The parthenogenetic development of ova in mammalian ovary and the origin of ovarian teratoma and chorionepithelioma. *J. A. M. A.*, 56: 1327, 1911.
- MARCHAND, FELIX: Missbildungen, in *Eulenburg's Realenzyklopaedic*, 9: 722, 1910.
- MEYER, ROBERT: Über Teratome (Dermoidcystome) des Ovariums mit freiem Beckenende und Extremitäten. *Arch. f. Gynäk.*, 123: 714, 1924-25.
- MILLER, JOHN: Henke-Lubarsch, *Handbuch der Pathologischen Anatomie*, 1937, vol. 7, part 3.
- MOOLTEN, S. E.: Hamartial nature of the tuberous sclerosis complex and its bearing on the tumor problem. *Arch. Int. Med.*, 69: 589, 1942.
- MOOLTEN, S. E.: Pathogenesis of congenital anomalies of the intrahepatic and extrahepatic bile ducts. Role of embryonic organizers in congenital malformations. *New York State J. Med.*, 727, 1943.
- NEEDHAM, JOSEPH: New advances in the chemistry and biology of organized growth. *Proc. Roy. Soc. Med.*, 29: 1577, 1936.
- NICHOLSON, G. W.: *Guy's Hospital Reports: Studies on Tumor Formation*, 1934, vol. 84, and 1934, vol. 85.
- RÉPIN, CHARLES: *Origine parthénogénétique des Kystes Dermoides de l'ovaire*, Thèse de Paris, 1892.
- SCHWALBE, ERNST: Die Morphologie der Missbildungen des Menschen und der Tiere. part 1, 1906, and part 2.
- SHATTOCK, S. G.: Acardiac acephalous ovarian embryoma. *Tr. Path. Soc. London*, 58: 267, 1907.
- SPEMANN, HANS: *Embryonic Development and Induction*. Silliman Memorial Lecture, New Haven, Yale University Press, 1938.
- SPEMANN, HANS AND MANGOLD, HILDE: Über Induktion von Embryonalanlagen durch Implantation artfremder Organisatoren. *Arch. f. mikr. Anat.*, 100: 599, 1924.
- VINEBERG, HIRAM N.: Teratoma, etc. November Meeting of New York Obstetrical Society, 1902; *Am. J. Obst. & Dis. Women*, 47: 97, 1903.

<sup>3</sup> For titles not mentioned in the Bibliography, see the bibliography to the article by J. Miller in Henke-Lubarsch, *Handbuch der Pathologischen Anatomie*, vol. 7, part 3.

## THE HEART IN EXPERIMENTAL SHOCK<sup>1</sup>

MYRON PRINZMETAL, M.D., AND H. C. BERGMAN, PH.D.

It is a well known fact that the heart may be adversely affected in shock. This is especially true if there is antecedent heart disease. Thus, so-called infectious shock, resulting from some such condition as pneumonia, seldom causes heart failure in a patient with a normal heart (1). But the same disease may cause or accentuate heart failure in patients in profound shock (2). Blumgart et al. (3) have recently described cases which developed cardiac infarction without coronary thrombosis following a prolonged shock state.

The altered hemodynamics in burn shock have recently been studied in this laboratory (4, 5). It has been found in burn shock that the reduced circulatory blood volume is due to two separate factors, capillary atony and local fluid loss. By transfusion experiments, it was shown that there is a toxic factor in the blood of burned animals which produces capillary atony. The capillary atony was characterized by an increase in number and diameter of open capillaries. For example, over three times the number of open and dilated capillaries were counted in the kidneys of burned rats as compared to non-burned animals. This capillary atony, which causes intense congestion of the viscera, is not due to heart failure or to anoxia for it was shown that the capillary congestion begins immediately after severe trauma. Measurement of the hemoglobin content of the viscera of shocked animals showed an increase in blood content. The relative importance of local fluid loss and the toxic factor varied with the character of the burn and the time after trauma. In certain types of burns the factor of local fluid loss was unimportant, and the capillary toxic factor accounted for all or most of the deleterious cardiovascular disturbances. Under other conditions, the factor of local fluid loss was operative in the first few hours after the burn, but the toxic factor became progressively marked and later dominated the clinical picture. Likewise, in shock produced by a crushing injury in dogs (6), in which the factor of infection is of primary importance, it was demonstrated that there are two factors causing the shock state: the capillary toxic factor which was the most important, and varying degrees of local fluid loss (7). Preliminary observations on tourniquet shock indicate that these two factors are involved in the resulting shock state (8).

It was the purpose of this study to determine if the same vascular disturbances occur in the heart and to determine if they account for some of the cardiac disturbances described in shock.

The methods of burning and of obtaining the bleeding volumes have been previously described (4). Twelve rats (160 to 200 grams) were completely anesthetized with ether; the skin over the occipital region of each rat was grasped

<sup>1</sup> From the Straus Research Laboratory, Cedars of Lebanon Hospital, and the University of Southern California Medical School.

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with a hemostat, and the animal was submerged up to the head in water at 100°C. for 30 seconds. This procedure produces very profound shock. These were compared with 12 non-burned controls. The hearts were removed under ether anesthesia and blotted free from obvious blood. In both shocked and control rats, following removal of the heart from the body, the length of time for the heart to stop beating was measured by observing the ventricular beat. Eight of the burned and eight control hearts were cut into 20 per cent urea solution, allowed to stand with occasional shaking for 24 hours, and the filtered fluid was examined colorimetrically for hemoglobin. The remaining hearts were prepared for histological study. Bleeding volume was measured by mopping up and weighing the blood which accumulated in the thorax when the heart was removed. Capillary and muscle fiber counts were made on cross sections of ventricular muscle stained as previously described to show red cells (4).

TABLE I  
*Comparison of cardiac changes in shocked and normal rats*

| EXPERIMENT   | SHOCK                           | CONTROL                       |
|--|---------------------------------|-------------------------------|
| Heart weight (as per cent of body weight).....                                     | 0.327 $\pm$ 0.030* $\pm$ 0.010† | 0.328 $\pm$ 0.015 $\pm$ 0.005 |
| Heart beat (seconds from time of removal from body to stopping of ventricle) ..... | 213 $\pm$ 15 $\pm$ 4            | 640 $\pm$ 92 $\pm$ 26         |
| Bleeding volume (as per cent of body weight).....                                  | 2.0 $\pm$ 0.16 $\pm$ 0.06       | 4.5 $\pm$ 0.05 $\pm$ 0.02     |
| Heart hemoglobin content (control = 100%).....                                     | 112                             | 100                           |
| Ratio of ventricular muscle fibers to capillary counts.....                        | 1.3 $\pm$ 0.4 $\pm$ 0.1         | 6.7 $\pm$ 4.2 $\pm$ 0.9       |

\* Standard deviation of a single observation.

† Standard error of the mean.

The results obtained are summarized in Table 1. Heart weights were the same in shocked and normal rats. The hearts of shocked rats stopped beating about three times sooner than normal rat hearts following removal. Bleeding volumes showed that the burned rats were in severe shock. The myocardium of shocked animals contained about 12 per cent more blood than untreated animals. The ratio of ventricular muscle fibers to capillary counts was about 5 times larger in control than in shocked rats. Figure 1 shows the comparative appearance of cross sections of myocardium from normal and shocked rats and illustrates the distribution and number of capillaries observed.

#### DISCUSSION

In shock there is a profound decrease in circulating blood volume and cardiac output. Terminally, there is a fall in arterial blood pressure. These factors, all of which are well known, cause a decrease in coronary circulation. But, because the work of the heart is also decreased in shock due to decreased cardiac

output, the decreased coronary flow does not appear to cause serious damage, since the energy requirements of the heart are reduced. However, it is apparent that the coronary circulation is often reduced more than the metabolic needs of the tissues. This would account for some of the altered cardiac function.

In the present study, the hearts of burned rats stopped beating about three times sooner than control hearts following removal from the body. This demonstrates that the musculature of the shocked rats is altered and less work is accomplished as a result of being deprived of coronary flow. It is possible that the altered cardiac function was produced either by ischemia or burn toxins before the heart was removed from the body. It is, however, unlikely that ischemia is very great during the short period of shock since analogous experiments (9)

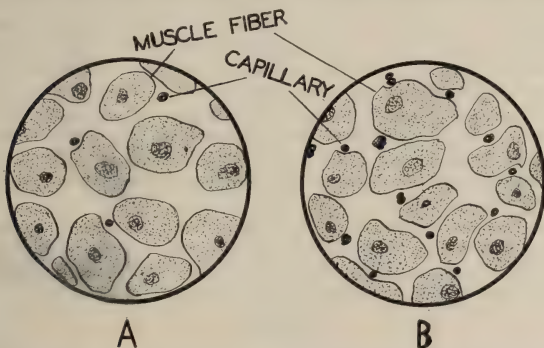


FIG. 1: Relative number of open capillaries and ventricular muscle fibers in the hearts of A—control rats, and B—shocked rats. Camera lucida drawing, magnification about 800  $\times$ . In these sections there are 13 open capillaries in the heart of a shocked rat as compared to 3 open capillaries in that of a control rat.

have shown that there is no fall in blood pressure during the first few minutes of shock; in fact, there is often a rise in blood pressure.

The extremely reduced bleeding volume of the burned rats demonstrates the severity of the shock induced.

It was shown that the heart of a burned animal contains appreciably more blood than that of a control animal. Many capillaries, normally dormant, are now wide open and contain increased quantities of blood. The evidence, however, indicates that this blood does not participate in the active circulation. In an acutely exsanguinated, shocked rat, the capillaries fail to contract and the blood is retained in these vessels. The retained blood soon loses its catabolic function and is of little or no value to cardiac function. In fact, this blood soon acquires catabolites in high concentration which are not removed from the heart. Thus, as a result, of this capillary atony, harmful catabolites may be retained in the tissues. Evidence in favor of this view is found in the disturbances in

metabolism occurring in all tissues of the body (10). Thus, the large number of open capillaries, while they may initially serve the requirements of the heart, soon may actually become detrimental.

It was previously shown that in early shock, the viscera weigh more than those of non-shocked animals due to the retention of blood (4). But later, despite the congestion and increased blood content, the organ weights equal those of non-shocked animals. The most likely explanation for this is that the tissues become dehydrated. It would seem plausible that dehydrated tissues cannot function as well as normal tissues. It is possible that a dehydrated heart cannot function as efficiently as a normal heart. In the present experiment, the animals were sacrificed in five minutes. This is too early for significant dehydration to occur.

Wearn (11) and Roberts, Wearn and Badal (12) have demonstrated by perfusion of surviving hearts with dye solutions that there is approximately one capillary per muscle fiber. They found the maximum number of capillaries to be in the ratio of 1.3 to 1.4 muscle fibers per capillary in ventricular muscle. In the present study, we have found an equivalent ratio in shock animals. Thus, it would appear that in severe shock, all cardiac capillaries are open. There are approximately five times as many open capillaries in the hearts of shocked rats as in control hearts. This method of studying shocked animals and the counting of capillaries might be a simple method of estimating the maximal number of capillaries in other organs.

The deleterious factors in clinical shock which can alter cardiac function are, thus, ischemia due to decreased coronary flow, capillary atony with retention of metabolites, and dehydration of the myocardium. These deleterious factors can well account for clinical disturbances of the heart in shock.

#### CONCLUSIONS

1. Severe shock was produced by scalding etherized rats. The anesthetized rats were submerged up to the head in water at 100°C. for 30 seconds.
2. It was shown that the function of the heart of shocked animals was reduced.
3. There were approximately five times as many open capillaries in the hearts of shocked animals as compared to control hearts.
4. By direct measurement, more blood was found in the myocardium of shocked rats as compared to that of normal rats.
5. The factor of capillary atony in shock is confirmed.
6. The possible clinical application of these findings is discussed.

#### REFERENCES

1. HITZIG, W. M., KING, F. H., BULLOWA, J. G. M., AND FISHBERG, A. M.: The circulation in lobar pneumonia with special reference to pulmonary edema. *J. Clin. Investigation*, 15: 452, 1936.
2. KATZ, L. N.: *Electrocardiography*, Philadelphia, Lea & Febiger, 1941.
3. BLUMGART, H. L., SCHLESINGER, M. J., AND ZOLL, P. M.: Multiple fresh coronary occlusions in patients with antecedant shock. *Arch. Int. Med.*, 68: 181, 1941.
4. PRINZMETAL, M., AND BERGMAN, H. C.: The nature of circulatory changes in burn shock. *Clin. Sc.*, in press.

5. PRINZMETAL, M., BERGMAN, H. C., AND HECHTER, O.: A demonstration of two types of burn shock. *Surgery*, 16: 906, 1944.
6. PRINZMETAL, M., FREED, S. C., AND KRUGER, H. E.: Pathogenesis and treatment of shock resulting from crushing of muscle. *War Med.*, 5: 74, 1944.
7. KRUGER, H. E., AND PRINZMETAL, M.: In preparation.
8. PRINZMETAL, M., AND BERGMAN, H. C.: In preparation.
9. JOHNSON, G. S., AND BLALOCK, A.: Experimental shock. XII. A study of the effects of hemorrhage, of trauma to muscles, of trauma to the intestines, of burns and of histamine on the cardiac output and on the blood pressure of dogs. *Arch. Surg.*, 23: 855, 1931.
10. LAM, C. R.: The chemical pathology of burns. *Surg., Gynec. & Obst.*, 72: 390, 1941.
11. WEARN, J. T.: The extent of the capillary bed of the heart. *J. Exper. Med.*, 47: 273, 1928.
12. ROBERTS, J. T., WEARN, J. T., AND BADAL, J. J.: The capillary-muscle ratio in normal and hypertrophied human hearts. *Proc. Soc. Exper. Biol. & Med.*, 38: 322, 1938.

# A DESCRIPTION OF AN EPIDEMIC CAUSED BY SALMONELLA TYPHIMURIUM AND THE BACTERIOLOGY OF THIS ORGANISM<sup>1</sup>

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The following communication not only describes, in detail, the epidemiological investigation of an outbreak of food poisoning in a small upstate community but also exhibits the accepted way in which a study of an epidemic gastrointestinal disease is approached. There follows an outline of this report in the form of a table of contents, which in a way displays the method in which the results of an investigation of an epidemic are presented:

## I. INTRODUCTION

## II. REPORT OF EPIDEMIOLOGICAL INVESTIGATION

### A. Epidemiological Description of County Involved

### B. Procedure of Investigation

1. Establishment of existence of epidemic
2. Finding common cause
3. Finding cause of infection
4. Searching for additional cases
5. Laboratory findings

### C. Report of an Associated Outbreak in Another Part of State

### D. Discussion

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It is, at this place, noteworthy of pointing out the similarity between the methods of management of a case by a clinician and an epidemiologist. They both make a diagnosis after evaluation of carefully obtained facts in the form of a history, physical and laboratory findings, and they then treat the patient symptomatically and with specific cures if available. The only difference between the two mentioned scientists is that the clinician's patient is a single individual while that of the epidemiologist is a community.

## I. INTRODUCTION

During the summer of 1940 there occurred in New York City an explosive outbreak among forty-seven persons, of an acute gastro-intestinal disease of unknown cause. All of the persons affected lived in the same part of the city.

<sup>1</sup> Reported for the New York State Department of Health, and read before The Harvard University School of Public Health May, 1941.



The signs and symptoms were nausea, vomiting, diarrhea, abdominal pain, fever, and, in some, occasional bloody stools.

After a preliminary investigation, members of the New York City Health Department determined that there was an unusual food item common to the diet of each person ill. Every patient had a history of having eaten a particular kind of smoked fish within a twenty-four hour period prior to the onset of symptoms. Some samples of this fish were found to be infected with *Salmonella typhimurium*.

Upon further investigation the department food inspectors traced this common food item to a single source. The individual purchases were found to be made in many retail shops, and each of these stores, in turn, had received its smoked fish products from a single wholesale distributing company in Brooklyn. This distributing company, the investigators learned, was connected with a similar company in Sullivan County, New York. At times, during periods of shortage of supply for distribution, the New York City establishment would receive shipments of smoked fish products from the one in upstate New York.

The New York City Health Department promptly informed the Middletown District State Health Office, in whose district Sullivan County lies, of the epidemic and its origin. As a result, the upstate Health Officer decided upon an immediate investigation of the locality throughout which the smoked fish company, (henceforth in this article to be indicated as the ABC Fish Company) was distributing its products, to ascertain the possible existence of an unreported outbreak of gastro-intestinal disease. The writer was assigned to this task and succeeded in uncovering an epidemic of food poisoning, with *Salmonella typhimurium*, the causative organism. The data secured in this investigation, together with an account of the bacteriological characteristics of *Salmonella typhimurium* are the material presented in this paper.

## II. REPORT OF EPIDEMIOLOGICAL INVESTIGATION

### A. *Epidemiological Description of Sullivan County*

To establish the existence of a specific epidemic in Sullivan County has more than its share of difficulties from the onset because of the nature of the county from an epidemiological point of view. The true population totals 36,176, the largest town or village in the entire county having less than 10,000 inhabitants (1). Because its landscape is very attractive and because of its proximity to New York City over one million people from this city vacation in this county during July, August and the first half of September. Almost every road, regardless of its type or size, whether it be concrete and wide or dirt and narrow, passes in front of summer homes, boarding houses, camps and hotels which temporarily house the vacationists.

Private water supplies which are not ordinarily used during the years, are turned on to meet the demands of the increased number of people. Both the engineering staff and the medical personnel in the district state health office have found a large number of these supplies to be potentially infectious on routine examinations.

The milk supply also presents a public health problem. Ordinarily, farmers who have an appreciable surplus of milk sell this dairy product to some large cooperative agency which disposes of it in a legally prescribed manner. During these boom population months, however, farmers have been found to sell their potentially infectious raw milk supply to hotels and camps in violation of the state sanitary code.

And finally there is the refrigeration factor. In a large number of boarding houses and summer camps, food preservation is attempted in poorly insulated ice boxes. Inspection of these boxes often reveals the absence of ice because delivery is not on schedule, or if a piece is in the box it is not large enough to cause sufficient cooling. Thus an opportunity is given organisms to multiply in any contaminated food.

All of the above-mentioned factors play an important part in the existence of numerous outbreaks of acute gastroenteritis in Sullivan County. During the months of July, August and the first half of September in 1939 and 1940 investigated outbreaks occurred almost daily in different parts of the county. An epidemiologist may go out and discover persons with recent or active acute gastroenteritis at almost any time.

With the situation such as described, an investigator may, therefore, expect difficulties from the onset in attempting to establish the existence of an epidemic due to the ingestion of a particular food.

There was one helpful guide, however. The type of gastroenteritis that occurred as a rule in Sullivan County was a mild one. The signs and symptoms were usually a low grade fever of 100°–101°F., nausea, vomiting and abdominal pain and they tended to disappear in about two days. The evidences for the diagnosis of the cases in New York City were more numerous and more severe. This point was kept in mind in the attempt to discover the presence of an outbreak of an acute gastroenteritis of a grave nature.

### *B. Procedure of Investigation*

1. *Search to establish existence of the epidemic.* On the afternoon of July 18th, the day of the receipt of the report of the outbreak in New York City, the writer visited the health officer of Monticello, the county seat of Sullivan County. This man knew of no one suffering from severe acute gastroenteritis. Conversations with the nine practicing physicians in town, however, and a visit to a nearby hospital in the vicinity revealed the presence of nineteen cases which seemed clinically to resemble those described in New York City.

Seventeen out of the nineteen patients had eaten smoked fish six to twenty-four hours before the onset of the illness. Fourteen had smoked butterfish, two had smoked carp and one had smoked whitefish (Table I). The remaining two had not taken any of this food product. These two cases have been omitted from the tables. They will be discussed later.

All of these seventeen patients were severely ill. Each one had diarrhea and vomiting, sixteen had nausea, fifteen had abdominal pain. In several the abdominal pain was of an intensity sufficient to warrant the use of opiates for

| CASE NO. | AGE | SEX | KIND OF SMOKED FISH EATEN | WHEN | DATE OF ONSET | SIGNS AND SYMPTOMS   | RETAILER OF FISH  | WHOLESALE OF FISH                             | REMARKS   |
|----------|-----|-----|---------------------------|------|---------------|--|-------------------|---|---|
| 1        | 47  | M   | Butterfish                | 7-13 | 7-13          | Fever, bloody stools, diarrhea, nausea, vomiting, leucocytosis, albuminuria, severe cramps | "A" in Woodridge  | ABC Fish Company                              | Only one in family who ate fish. No others ill  |
| 2        | 28  | F   | Butterfish                | 7-13 | 7-14          | Headache, high fever, severe abdominal cramps, nausea, vomiting, diarrhea                  | "B" in Monticello | ABC Fish Company                              | Only two in family who ate fish. No one else ill  |
| 3        | 28  | M   | Butterfish                | 7-13 | 7-14          | Same as above  | Same as above     | ABC Fish Company                              | Only one in family who ate fish at this time. No one else ill   |
| 4        | 59  | M   | Butterfish                | 7-13 | 7-14          | Diarrhea, nausea, vomiting, severe abd. cramps   | Same as above     | ABC Fish Company                              | Only one in family who ate fish. No one else ill  |
| 5        | 12  | F   | Whitefish                 | 7-13 | 7-14          | Diarrhea, vomiting, high fever, severe abd. cramps   | "C" in Monticello | ABC Fish Company                              | Only one in family who ate fish. No one else ill  |
| 6        | 8   | F   | Butterfish                | 7-13 | 7-14          | High fever, diarrhea, vomiting, nausea   | "D" in Monticello | ABC Fish Company essentially and 3 others     | Only one in family of 3 who ate fish. Others well   |
| 7        | 40  | F   | Butterfish                | 7-14 | 7-15          | Diarrhea, nausea, vomiting, high fever, headache   | Same as above     | ABC Fish Company essentially and three others | Only one in family who ate fish. No others ill  |
| 8        | 38  | F   | Carp                      | 7-16 | 7-16          | High fever, vomiting, nausea, severe abd. cramps, diarrhea                                 | "E" in Monticello | ABC Fish Company                              | Only two in family who ate fish. No others ill  |
| 9        | ?   | F   | Carp                      | 7-16 | 7-16          | Same as above  | Same as above     | ABC Fish Company                              | Only two in family who ate fish. No others ill  |
| 10       | 25  | M   | Butterfish                | 7-16 | 7-16          | Same as above and bloody stools  | Same as above     | ABC Fish Company                              | Only two in family who ate fish. No others ill  |
| 11       | 25  | M   | Butterfish                | 7-16 | 7-16          | Same as above  | Same as above     | ABC Fish Company                              | Only one in family who ate fish at this time. Father also ill three days previously. See case no. 4 above |
| 12       | 28  | F   | Butterfish                | 7-16 | 7-17          | Fever, diarrhea, severe abd. cramps, nausea, vomiting, albuminuria, leucocytosis           | "B"               | ABC Fish Company                              | Only one in family who ate fish at this time. No one else ill   |
| 13       | 35  | F   | Butterfish                | 7-17 | 7-17          | Bloody stools, diarrhea, severe abd. pain, nausea, vomiting                                | "F" in Monticello | ABC Fish Company                              | Only one in family who ate fish at this time. No one else ill   |
| 14       | 65  | F   | Butterfish                | 7-16 | 7-17          | Severe abd. cramps, diarrhea, bloody stools, nausea, vomiting, fever                       | "E" in Monticello | ABC Fish Company                              | These four people, in a family of five, ate the fish and became ill. The remaining one is well            |
| 15       | 45  | F   | Butterfish                | 7-16 | 7-17          | High fever, severe abd. cramps, nausea, vomiting, diarrhea                                 | Same as above     | ABC Fish Company                              |   |
| 16       | 67  | F   | Butterfish                | 7-16 | 7-18          | Same as above  | Same as above     | ABC Fish Company                              |   |
| 17       | 55  | F   | Butterfish                | 7-16 | 7-18          | Same as above  | Same as above     | ABC Fish Company                              |   |

relief. Fourteen suffered with a fever from 101°F. to 105°F., four with bloody stools and three with headache. Four persons were hospitalized and the remainder was treated at home.

Table I shows that the ages of those ill ranged from eight to sixty-seven years. There were no significant variations in attack rates according to age. Five were males and twelve were females.

Stool specimens were obtained from each patient and were immediately mailed, in special containers with 30 per cent glycerol, to the Division of Laboratories of the State Health Department in Albany. The reports will be discussed later.

*2. Steps taken to find common cause.* Once the existence of an epidemic similar to the one in New York City was established, it was then necessary to trace the suspected food product to a common source. Each patient, or the family of the patient, was carefully questioned concerning the place of purchase of the smoked fish. A total of six retailers were named. Each store was visited and the proprietor personally seen. All made their purchases from a single wholesale company located in the same county, and this was the very same company to whose branch office in New York City the outbreak there was traced. Five of the six retailers purchased their smoked fish products exclusively from this ABC Fish Company. One retailer purchased not only from this wholesale house, but also from three additional companies located in New York City (Table I).

*3. Steps taken to find cause of infection.* Since all evidence for the common cause of the epidemic pointed to a single type of food which was distributed by one firm in the locality, the writer visited this wholesale house. The plant structure was an old metal and wood one-story building with its floor on the ground level. It had the appearance of an ancient barn. The walls sagged in places. The front entrance had no door. The rear entrance had an improperly fitted framework which opened out toward a field in which were piles of old fish crates.

Inside the building was a fish cleaning room, a combination sales and packing room, a small chamber for refrigeration, and three completely enclosed cubicles in which the fish were smoked. Cement was the flooring material of the first-mentioned room. The floor of the sales and packing room was of wood, was warped in some places, had pieces missing in others, and was covered with saw dust.

The general impression was that of untidiness. The shelves and table tops were dirty. Articles of food and jars were scattered about. There seemed to be no order in the place.

The owner was overwrought because the smoked fish products in his New York city branch had been embargoed by the health officials there, and in the tirade that followed stated, "I don't know why people are making such a fuss about a little bellyache. I was so sick last week I thought I was going to die." Further questioning relating to this statement revealed that the proprietor had severe abdominal cramp-like pains for several days commencing on July 14th and he had been eating smoked fish. A stool specimen was obtained from this man

that same afternoon as well as from the six employees in the plant on the following day.

The processes involved in the preparation of the final smoked fish product were observed in some of their parts and informed of in others. Chubs, which were sold as small whitefish were a fresh water fish. They were delivered from six different distributing companies in New York City to the plant in a fresh state, packed down in ice chips in crates. These fish were then soaked in a large barrel into which poured a constant stream of water from a hose. The overflow spilled over the barrel top onto the floor and out through a drain. The water distribution source was the village reservoir.

After the soaking process, the viscera were removed by hand, and the fish were then placed in a forty per cent saline solution for six hours. Following this procedure each fish was suspended by the head on a small hook on a large rack in one of the three smoking rooms. Here the fish were dried over gas fire coming from many fire jets in several pipes running along the floor. After the drying process, several charcoal burners were placed in the room, and the fish were encircled by the smoke. And finally, they were layered between screened wood shavings which burned or glowed for about an hour. The end product was placed in boxes which were stored in a refrigerated room maintained at a temperature of 48°F. (This was the reading at the time of the investigation.)

The large whitefish, a fresh water fish, was delivered to the plant in a frozen state from two distributing companies in New York City. Butterfish, a salt water fish, was delivered also in a frozen state from another distributing company in Brooklyn. These fish were stored as long as one year in the frozen state. Before a batch was to be smoked in the same manner as described previously, they were thawed out by being placed in a barrel into which a continuous stream of cool water flowed.

Carp, a fresh water fish, was purchased by the ABC Fish Company from the same distributing houses from which the above-mentioned chubs were obtained. The carp were frozen by the company after delivery in Monticello and the stock was drawn upon during a one-year period as it was needed for smoking. When used, the fish were thawed out and smoked as described previously, but in addition, paprika, garlic and pepper were added before the smoking process.

The vats used for the salting of the fish drained into a sewer line which was connected in common with a toilet drain. This sewer line, in turn, drained into a ditch near to the plant. A representative from the New York City Health Department had a sample of the ditch water examined, and it revealed *Salmonella typhimurium* on bacteriological examination (2). This finding will be discussed later.

Representatives from the Department of Agriculture and Markets of New York State visited the ABC Fish Company. They obtained specimens for laboratory analysis at this point. The food inspectors then traced and checked the crates of fish to the distributing companies in New York City. Specimens of fish were also taken at this point. It might be stated now that laboratory analyses of the different samples revealed nothing of interest.

It was learned that the original source of the different kinds of fish were two



companies in Canada. The minister of Health there was made acquainted with the situation and an investigation for similar outbreaks traced to these companies



FIG. 1

was made. This search in Canada revealed that no other epidemic involving fish from these companies had been known.

4. *Steps taken to find additional cases.* Further conversation with the proprietor-manager of the smoked fish plant revealed that sales of his products were constantly made not only to the investigated retail stores in Monticello, but also to retail stores and hotels in the entire county and part of an adjoining county. In addition, at the end of each week a large portion of the unsold smoked fish was taken in an unrefrigerated truck along the hot, dusty state Route 17 down to the branch company in Brooklyn.

An attempt was made to discover cases of the disease in the areas of distribution. The health officer in each region was reached by telephone and the physicians in the nearby large village of Liberty were personally visited. No new cases were found. Apparently the outbreak was confined entirely to Monticello and its environs, and Brooklyn, N. Y.

Figure 1 is a map picturing the distribution area of the fish products and the regions in which cases were found.

5. *Laboratory Findings.* The stool specimens taken from the proprietor-manager of the smoked fish company in Sullivan County and from one of his employees as well as from each of the seventeen persons ill, were all reported positive for the presence of organisms belonging to the *Salmonella* group. These bacteriological examinations were done by bacteriologists in the Division of Laboratories and Research of the New York State Department of Health in Albany, New York.

Four of the above group positive specimens were randomly taken at the laboratory and followed through for the specific member of the group. Each of the four revealed the presence of *Salmonella typhimurium*. One of these four specimens came from the proprietor-manager of the smoked fish company.

All of the positive specimens were not analyzed bacteriologically for the specific organisms of the *Salmonella* group because of the intricacies of the procedure and scarcity of the amount of the sera necessary for the identification of individual species. The bacteriology of this group will be described later.

The stool specimens are forwarded to the laboratory in the special containers supplied by the Division of Laboratories and Research. The specimens are obtained from persons in several different ways. Occasionally, if the situation demands, a specimen is obtained by the health investigator in the field perhaps after patient waiting. Frequently the family physician undertakes the job or the staff in a hospital, if the patient is hospitalized. Every now and then the person himself or some responsible member of the household is asked to send in the specimen. Under such circumstances the responsible person is instructed to place a pea sized amount of the stool into a given container containing glycerol solution, repack the container and drop it into the nearest mailing box. It is advisable for the field man to fill out the enclosed laboratory blank and place the necessary postage on the carton. This procedure insures better cooperation. If, for some reason, it is necessary to be assured of the authenticity of a specimen, a colored lycopodium capsule may be given by mouth in the presence of the field investigator for the purpose of identifying the stool. Lycopodium is a powder prepared from the spores of the moss, *Lycopodium clavatum* and other species

of *Lycopodium*. It is an innocuous substance which shows up, unchanged, in the stools.

*C. Summary of Report of Outbreak in Brooklyn, N. Y.*

The following are extracts from the report (2) of the outbreak in New York City, investigated by the Department of Health in that city.

"On July 16, 1940, several cases of acute gastroenteritis in Brooklyn were reported to the Department of Health. Within the next few days the reported cases rose to 47, in 18 separate families. Symptoms in all patients consisted of abdominal pain, diarrhea, and high temperature. In some cases, marked prostration occurred, and 6 persons were so seriously ill that they were removed to hospitals."

"The others remained at home under medical care. Two of the patients died, one a boy of 5, who became ill on July 13 and died on July 17; the other a man of 51, also became ill on July 13 and continued to have symptoms until July 28, when he too died."

"It was quickly determined that the families affected had eaten smoked fish products purchased in 12 different Brooklyn neighborhood delicatessen stores. From those retail stores the source of the smoked fish was traced to a wholesale smoked fish establishment with retail outlets throughout Brooklyn. The smoked fish in question were whitefish, butterfish, and carp, and had been smoked in a plant in upstate New York, about 100 miles away from New York City. It had been distributed both in that vicinity and to retailers in Brooklyn. After remaining in delicatessen stores for varying periods of time up to several days, this product, which is customarily eaten without any further cooking, was sold to persons who came down with symptoms of food poisoning within a few hours after consumption of the smoked fish."

"As soon as the source of the fish was traced, inspectors of the Health Department embargoed smoked fish (approximately 1000 lbs.) from this plant found in the retail outlets. This fish was later destroyed."

"Chemical examinations of all specimens of fish were negative for inorganic or organic poisons. Specimens for bacteriological examination included stools from patients and from food handlers in retail and wholesale establishments; samples of fish from homes of patients, retail stores, and wholesale plants. From all of these sources a similar organism was recovered, *Salmonella typhimurium*, as follows:

|  |    |
|--|----|
| Patients (consumers).....                | 14 |
| Patients (retail foodhandlers) .....     | 3  |
| Patient (wholesaler).....                | 1  |
| Processor (not sick).....                | 1  |
| Fish (whitefish, butterfish, carp) ..... | 5" |

"Autopsy on the 51 year old fatal case revealed that the entire gastrointestinal tract exclusive of the stomach had small areas of superficial hemorrhage. There was marked desquamation of the mucosa of the ileum; some areas were a dark

greenish brown in color with numerous scattered hemorrhages. There were no gross ulcerations, no lymphoid hyperplasia, and no enlargement of the mesenteric lymph nodes. The large bowel showed moderate congestion of the spleen, adrenals, liver, and kidneys. *Salmonella typhimurium* was isolated from the lung."

#### *D. Discussion of Findings and Association with Epidemic in New York City*

After reviewing the above information, it is the writer's opinion that the smoked fish has been the offending food, and the infecting organism is the *Salmonella typhimurium*. The seventeen cases listed in Table I were all severely ill and all had eaten smoked fish within a twenty-four hour period previous to the time of onset of signs and symptoms referable to the gastrointestinal tract. A stool specimen from each patient contained organisms of the paratyphoid-enteritidis group. Three of these specimens on further analysis revealed, specifically, *Salmonella typhimurium*.

It is true that in the attempt to discover cases according to the technique previously described, two equally severe cases of acute gastroenteritis were encountered with no history of having eaten smoked fish, but it is felt, as stated before, that in any investigation in a region like Sullivan County where there are numerous outbreaks of acute gastroenteritis, random cases will be discovered by chance questioning. The cause of the illness in these two persons remained unknown.

In each one of the families in which illness occurred only those who ate the fish at the time were ill. All the other members of the different involved families remained well.

Since this type of fish is eaten as purchased, with no additional dressing or preparation, any possible closely associated food may be eliminated. Either milk, bread, butter or water, common articles of diet and possibly eaten with the smoked fish may be discounted as having been the offending food because they have been articles of diet eaten by members of the family who have not become ill.

And finally, the evidence directly associated with the smoked fish company well establishes the offending food to have been the smoked fish, and the infecting organism, *Salmonella typhimurium*. Each fish purchase made by the families in which illness occurred was traced to one of six retailers in town. Each one of these retailers purchased smoked fish from the ABC Fish Company in Sullivan County. Five of the six made their purchases exclusively from this one company. The sixth made additional purchases from three other companies.

Stool specimens from the owner of the smoked fish company and one of his employees contained organisms belonging to the paratyphoid-enteritidis group. Further analysis of the proprietor's stool specimen revealed specifically *Salmonella typhimurium*.

The evidence that this outbreak is associated with the one in New York City is clear. Forty-seven people in eighteen different households were ill. Each one affected had eaten smoked fish and each purchase of this food was

traced to one of twelve retailers who in turn purchased from a common smoked fish company. This company and the one in upstate New York were owned by the same person and weekly shipments of the products were sent from the firm in Sullivan County to the Brooklyn branch.

Then there is the New York City evidence. Samples of the smoked fish remaining in some of the patients' homes, in the retail stores, and at the Brooklyn fish smoking establishment, revealed the presence of *Salmonella typhimurium*. A similar organism was recovered from the stools of fourteen patients and five foodhandlers.

It is interesting to note that those who became ill in Sullivan County ate fish purchased at a retail store. Thousands of pounds of this commodity are sold weekly by the company to a large number of hotels and camps in Sullivan County and yet not a case was reported at any of these places. In the retail shops the fish lay on the counter without refrigeration and under burning electric lights. One proprietor admitted that the fish may remain on the counter for almost a week and are placed in the refrigerator at night only. This procedure would permit organisms, which in small numbers may not cause illness, to incubate and produce a sufficiently large dose to cause disease. On the other hand, the loads of fish when delivered to the hotels and camps are placed in a refrigerator thus checking any incubation after a possible contamination from some source.

The ultimate source of this epidemic is difficult to state. The proprietor of the company was ill and his stool specimen contained the *Salmonella typhimurium*. Two more foodhandlers in Brooklyn were ill and their stools revealed the same organism. Some more employees in both plants had positive stools without the history of illness. Whether one of these men in the Sullivan County establishment caused the infection of a batch of fish which in turn caused the outbreak in both places or whether all these men became infected by the eating of the contaminated fish just as did the purchasers or their families is difficult to say. Further, whether the fish became contaminated during the salting process in the vats which might have had a back flow of *Salmonella typhimurium* contaminated sewer water from one of the infected foodhandlers, or whether the foodhandler became infected from eating already contaminated fish, and then, in turn, adding the offending organism to the sewage, is a matter of guessing.

As stated in the physical description of the Sullivan County firm, the place was grossly unsanitary. The smoking room opened out to a field. The doors could not be shut tightly. It is conceivable that rats or field mice may have gained entrance and contaminated a batch of fish with infected droppings during any of the steps in the process of preparing the food. It is not known how much germicidal action is obtained by the smoking process. The thermal death point of *Salmonella typhimurium* is not high. Thirty minutes at 60°C. will destroy this strain.

It would have been interesting to have caught some of the rats in the field behind the plant structure and examine them for *Salmonella typhimurium* infection. This, however, was not done.

Another possible ultimate source of the outbreak may have been a contamina-



tion of the fish products with a rat "poison" containing *Salmonella* organisms. This material is sold commercially although its sale is prohibited in some states. The use of this material in the plant, however, was denied by the owner.

### *E. Steps Taken to Control Spread*

The last illness in the epidemic occurred on July 18th. The epidemiological investigation did not offer a truly definite source until the twenty second of the same month. Many hundreds of pounds of fish were sold during the epidemic period and the period of investigation. Because no new cases were reported between the eighteenth and twenty second even though all the physicians in the locality had been informed of the outbreak, the New York State Department of Health decided not to embargo the products of the company. It was thought that only one batch of fish which was already sold had been contaminated.

The carrier state of the food handlers offered little difficulty. The owner was advised not to touch any of the food products until four successive stool specimens were obtained free from organisms of the *Salmonella* group. The other handler, an employee, whose feces revealed the organism, left the firm.

The carrier state in foodhandlers may offer a serious problem. In a recent large outbreak of a severe acute gastroenteritis traced to turkey infected with *Salmonella typhimurium*, the carrier state of 195 persons ill was followed. 31.9 per cent harboured the organism for more than two weeks, 21.0 per cent more than three weeks, 9.2 per cent more than four, 2.1 over two months, one person or 0.5 per cent over four months (7).

Finally, all possible measures were taken to prevent a similar outbreak. The entire structure of the Sullivan County plant building was renovated and made rat proof.

## III. BACTERIOLOGY OF SALMONELLA (TYPHOID-PARATYPHOID)

### *A. Classification and Group Nomenclature (3)*

The classification of the *Salmonella* Group is now based on the antigenic structure of the species, or types, of which it is comprised. The bacilli in this group are mostly flagellated organisms. The flagellar antigen is called the H antigen, and the somatic the O antigen. These components can be tested for separately. In a given species or type there is usually more than a single H and O antigen. The determination of the antigenic structure of a particular species of *Salmonella* organism may involve the identification of eight different antigenic components. The method usually used now is that of direct agglutination of H and O suspensions with antisera which by previous absorption with appropriate antigenic types, have been rendered specific for one or other antigenic component, or a small group of such components. Up to the present time thirteen or more different somatic antigens, twenty-eight specific flagellar antigens, and six or more group flagellar antigens have been identified.

The *Salmonella* Subcommittee of the International Society for Microbiology has adopted the terminology introduced by Kauffmann in which each member of the *Salmonella* group is allotted an antigenic formula based on a system of

labelling. The somatic (O) antigens are accorded Roman numerals, the specific flagellar (H) antigens are accorded small letters, and the group flagellar (H) antigens are accorded arabic numerals. Thus the formula for *Bact. paratyphosum* C is VI, VII: c: 1, 4, 5.

The *Salmonella* Group, as a whole, has been divided into sub-groups, each of which shares a common somatic antigen. Where more than one somatic antigen is present, one of these antigens is regarded as determining the sub-group to which the species, or type, concerned shall be allocated.

A practice has arisen of giving each new antigenic type in the *Salmonella* group a separate specific name. The convention that has been universally followed is to give the new organism the name of the place in which it was first isolated such as *Bact. aertrycke*. In some instances the more familiar form of a specific name has been retained such as *Bact. typhosum*. There are now over ninety differently named species each one having its own formula.

### *B. Salmonella Typhimurium* (3)

The *Salmonella typhimurium* (Antigens IV, V:i: 1, 2, 3) is a natural pathogen in rodents, particularly mice, in which it causes a typhoid like disease. This organism is the same as *Bact. aertrycke* which was originally isolated from a case of acute gastroenteritis in man by de Nobele in 1898. It is under the name of *Bact. aertrycke* that it appears in almost all the recent and current literature. It is also identical with *B. pestis caviae*, described by Wherry (1908) as the cause of an epidemic disease in guinea-pigs, and with the bacillus that Nocard (1893) isolated from a parrot suffering from psittacosis and named *Bact. psittacosis* under the mistaken impression that it was the cause of that disease. The same organism is frequently referred to in German literature as the "Breslau bacillus."

*Sal. typhimurium* is pathogenic for man as well as for animals and is the most frequent cause of outbreaks of *Salmonella* food poisoning. It commonly gives rise in man to an acute gastroenteritis, not infrequently fatal, but it occasionally causes a prolonged fever of the enteric type. Although it has most often been recorded as causing epidemic disease in mice and rats, it is naturally pathogenic for many other animal species. In addition to causing infections in guinea pigs and parrots, it has been isolated from epidemics in sheep, chicks, pigeons, turkeys and canaries. It also causes infections in ducks, and has been isolated from ducks' eggs. It has been occasionally isolated from pigs that have died of swine fever.

### *C. Identification of the Salmonella Group in Fecal Specimens* (4, 5)

The feces may be considered satisfactory for examination only when the specimen is received within four days after collection in approximately ten times its volume of a satisfactory standardized preservative such as buffered 30 per cent glycerol solution or within a few hours after collection if no preservative is used.

By resorting to sugar fermentation reactions, motility observations, and indol production and reaction in milk the bacteriologist can determine whether mem-

bers of the *Salmonella* group are present. Following this procedure, an attempt is made to determine the group in the Kauffmann-White Schema (described above) to which the organism belongs. This is done by agglutination tests using a multivalent *Salmonella* group serum which is prepared by pooling sera produced with species representative of the various groups in the above schema. This multivalent serum agglutinates all but a few of the less common species.

Then comes the final step. After determining the group to which the organism belongs, the species is identified by agglutination with its homologous specific antiserum.

What is the value of determining the species? In the treatment of the patient there is none at present. In epidemiological investigations, however, the identification of the exact species is of great importance. For example, in the outbreak described in this paper, knowing the specific organism aided in definitely associating the epidemic in Sullivan County with the one in New York City.

More often, the identification of the species can be undertaken only by a few because the specific sera are so difficult to produce. These sera and cultures are supplied by Dr. Kauffmann at the International *Salmonella* Center in Copenhagen, Denmark to thirty-seven *Salmonella* Centers in the world. Of the thirty-seven there are at least three in the United States. These are located in New York City, Albany, N. Y. and Lexington, Ky. (6).

#### IV. SUMMARY

1. This paper describes, epidemiologically, an outbreak of food poisoning caused by the ingestion of smoked fish infected with *Salmonella typhimurium*.
2. The association of this epidemic with a similar one in Brooklyn, New York is shown.
3. The bacteriology of the *Salmonella* group is reviewed with specific detailed reference to the *Salmonella typhimurium*.

#### V. BIBLIOGRAPHY

1. Fifty-ninth Annual Report of the New York State Department of Health, Division of Vital Statistics, 1938.
2. KLEEMAN, IRVING; FRANT, SAMUEL; AND ABRAHAMSON, ABRAHAM E.: Food Poisoning Outbreaks Involving Smoked Fish—their Epidemiology and Control, *Am. J. Pub. Health*, 32: 2, February, 1942.
3. TOPLEY, W. W. C., AND WILSON, G. S.: *The Principles of Bacteriology and Immunity*, ed. 2, Baltimore, William Wood and Co., 1936, p. 563.
4. From a paper presented by Marion B. Coleman from the Division of Laboratories and Research, New York State Department of Health, Albany at the mid-year meeting of the New York State Association of Public Health Laboratories, November 1, 1940.
5. WADSWORTH, AUGUSTUS B.: *Standard Methods of the Division of Laboratories and Research of the New York State Department of Health*, ed. 2, Baltimore, Williams & Wilkins Co., 1939, p. 173.
6. BROOKS, R. ST. JOHN: Discussion on *Salmonella* Infections, *Proc. Roy. Soc. Med.*, 33: 370, 1940.
7. Personal communication with Stafford Wheeler, Department of Epidemiology, Harvard University.

# HYPERPARATHYROIDISM

## REPORT OF A CASE

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The classic picture of hyperparathyroidism with its characteristic bone changes is too well known to require further description. The initial clinical recovery in a patient with osteitis fibrosa cystica, following removal of a parathyroid adenoma by Mandl (1) in 1925, clearly and dramatically established the relationship between increased parathyroid activity and the disease of the skeleton described by v. Recklinghausen. Reports of early investigators abroad (2, 3) and in this country (4, 5, 6) gave ample confirmation to this discovery, and the work of these men and others evolved the abnormal metabolic pattern of hypercalcemia, hypophosphatemia, hypercalciuria and increased blood phosphatase on which the diagnosis rests.

Although the presence of renal calculi had frequently been noted in association with Recklinghausen's disease in the past, it remained for Albright and his group (6, 7) to emphasize the significance of this lesion in hyperparathyroidism. They described several cases of recurrent urolithiasis without bone lesions, which on investigation disclosed the typical chemical pattern of hyperparathyroidism and at operation revealed adenomas of the parathyroid gland. Routine blood calcium and phosphorus studies at other clinics (8, 9) on patients with renal calculi have brought to light a number of cases of hyperparathyroidism which would never have been suspected otherwise. This does not imply that all renal calculi have this pathogenesis. As a matter of fact, only a small percentage of all calculi are actually due to hyperparathyroidism, and this has been variously estimated at from 0.2 to 4 per cent (8, 10). These findings become more readily understandable if one considers the development of renal calculi as an early manifestation of hyperparathyroidism, while the bone changes are an advanced or late manifestation of the disease. The following quotation from Snapper's book (11) clearly expresses this concept: "The generalized decalcification with multiple giant cell tumors and bone cysts must be a late stage of the disturbance of calcium and phosphorus metabolism due to hyperparathyroidism. In earlier stages of hyperparathyroidism the decalcification is not yet visible on the x-ray, although the calcium and phosphorus metabolism may already be completely upset. The skeleton of an adult contains about 900 gm. of calcium. Even when the calcium balance is strongly negative, the daily loss of calcium hardly ever exceeds 0.5 gm., at the utmost 1 gm. of calcium. Several months, perhaps even years, must elapse before demineralization of the skeleton can be discovered by x-ray examination. Thus, in hyperparathyroidism frank symptoms and signs, depending on hypercalcemia and the excess of calcium and phosphorus excreted in the urine, may occur before the presence of an affection of the skeleton has

made itself felt. This explains why in patients with hyperparathyroidism renal stones may develop before subjective, or even objective involvement of the skeleton."

The presence of renal calculi may furthermore lead to renal insufficiency through the development of pyelonephritis and secondarily contracted kidneys. However, another type of renal impairment has been reported by Albright (7). This may occur even in the absence of renal stones and is due to the precipitation of calcium phosphate in the renal parenchyma, most frequently in the collecting tubules. "Inflammation," sclerosis and contraction of the kidneys ensue, and the resulting picture is often clinically indistinguishable from chronic glomerular nephritis. Roentgenographic examination of the abdomen will sometimes reveal stellate groups of fine punctate shadows outlining the kidney pyramids, while pathological examination of these kidneys shows sclerotic changes associated with small areas of calcification. To this type of renal involvement in hyperparathyroidism, Albright (6) has given the name, *nephrocalcinosis*.

The following case is an instructive example of the early type of hyperparathyroidism, in which the symptoms and signs are almost purely urologic in character, and evidence of bone involvement is either insignificant or else completely absent. It illustrates further early, but definite, evidence of renal impairment, not pyelonephritic in type, with restoration of normal renal function after the removal of a large parathyroid adenoma.

#### CASE REPORT

*History:* I. S., a 56 year old male, first presented himself for examination on May 6, 1944. His main complaint consisted of easy fatigability which had been present for about five years and had become worse during the past few months. There were no bone pains and no history of fractures. He had moderate urinary frequency, voiding every one to two hours during the day and three times at night. These symptoms had been present for the past seven years but were not progressive in character. There were no other urinary symptoms and no polydipsia.

In May 1937, after a five day history of severe right loin pain, he was hospitalized, and an impacted right ureteral calculus was discovered. A typical ureterotomy was performed with complete relief of symptoms. A routine urine examined at this time showed a specific gravity of 1.030. There was no albumin and microscopic examination revealed only an occasional red blood cell.

His next hospital admission occurred in April, 1941, for severe left renal colic. Examination disclosed a left ureteral calculus which was pushed back into the kidney pelvis by cystoscopic manipulation. The urinary specific gravity was 1.022 with a very faint trace of albumin and a few red blood cells. The blood pressure was 135 systolic and 80 diastolic. One month later he was readmitted to the hospital with a recurrence of symptoms and a left ureterotomy was performed for removal of an impacted left ureteral calculus. Two urine examinations revealed specific gravities of 1.020 and 1.030, a trace of albumin, and a few red blood cells. There was no pyuria and the blood pressure was 110 systolic and 68 diastolic. A chemical analysis of the calculus showed magnesium ammonium phosphate and calcium carbonate.<sup>1</sup> He subsequently had mild attacks of right renal colic in 1942 and again in February 1944.

<sup>1</sup> In those cases of proven hyperparathyroidism in which a chemical analysis of renal calculi has been performed, the usual finding has been calcium phosphate. In a few cases calcium oxalate stones have been reported.



*Examination:* The physical examination was essentially negative except for the findings in the neck. Just above the inner end of the right clavicle, in the region of the lower pole of the right lobe of the thyroid gland, there was a cystic swelling about the size of a small plum. At this time it was impossible to decide whether the mass was thyroid or parathyroid in origin. There was no bony tenderness or deformity. The blood pressure was 110 systolic and 64 diastolic. There was a slight enlargement of the prostate gland.

*Laboratory data:* Blood analysis done at a private laboratory revealed the following: Urea nitrogen 20.8 mg. per 100 cc., calcium 15.6 mg., phosphorus 2.2 mg. and phosphatase 17.6 King-Armstrong units (normal values for adults are 5 to 10 units). He was then ad-

TABLE I  
Laboratory Data

| DATE                | BLOOD CHEMISTRY        |      |     |                         |                    |                  | URINARY FINDINGS |             |        |
|---------------------|------------------------|------|-----|-------------------------|--------------------|------------------|------------------|-------------|--------|
|                     | Urea<br>N <sub>2</sub> | Ca   | P   | Phos-<br>pha-<br>tase   | Serum<br>Protein   | CO <sub>2</sub>  | Specific Gravity | Albumin     | P.S.P. |
|                     | mg. per 100 cc.        |      |     | units<br>per 100<br>cc. | gm. per<br>100 cc. | vol. per<br>cent |                  |             | %      |
| May 1937.....       |                        |      |     |                         |                    |                  | 1.030            | Negative    |        |
| April 1941.....     |                        |      |     |                         |                    |                  | 1.022            | Faint trace |        |
| May 1941.....       |                        |      |     |                         |                    |                  | 1.020            | Trace       |        |
|                     |                        |      |     |                         |                    |                  | 1.030            | Trace       |        |
| May 6, 1944.....    | 20.8                   | 15.6 | 2.2 | 17.6                    |                    |                  |                  |             |        |
| May 31, 1944.....   | 15.0                   | 12.5 | 2.1 | 22.00                   |                    |                  | 1.012            | Faint trace |        |
| June 2, 1944.....   |                        |      |     |                         |                    |                  | 1.014-1.018†     | Faint trace |        |
| June 8, 1944.....   |                        |      |     | 21.0<br>6.0†            |                    |                  | 1.008            | Negative    |        |
| June 17, 1944.....  |                        |      |     |                         | 6.3                |                  |                  |             | 33     |
| *June 20, 1944..... |                        | 13.6 | 1.9 | 6.1                     |                    |                  | 1.010            | Faint trace |        |
| June 21, 1944.....  | Operation              |      |     |                         |                    |                  |                  |             |        |
| June 22, 1944.....  |                        | 11.7 |     |                         |                    | 47.2             | 1.010            | Faint trace |        |
| June 24, 1944.....  |                        | 10.1 |     |                         |                    | 55.5             | 1.010            | Faint trace |        |
| July 5, 1944.....   |                        | 10.0 |     |                         |                    |                  |                  |             |        |
| Oct. 10, 1944.....  | 18.8                   | 9.1  | 2.7 |                         |                    |                  | 1.026-1.028†     | Negative    | 73     |

\* Blood Chemistry done by Dr. Bodansky. The phosphatase is reported in Bodansky units. Other results are reported in King-Armstrong units.

† Concentration Test.

‡ Acid Phosphatase.

mitted to the hospital for further investigation, where the following laboratory data were obtained: Hemoglobin, 95 per cent; red blood cells 5,130,000; white blood cells, 5,900 with 46 per cent segmented and 17 per cent non-segmented polymorphonuclear leucocytes, 35 per cent lymphocytes and 2 per cent eosinophiles. The basal metabolic rate was plus 3 per cent. Blood chemistry determinations showed urea nitrogen 15 mg. per 100 cc., calcium 12.5 mg., phosphorus 2.1 mg. and phosphatase 22 King-Armstrong units. The serum proteins were 6.3 gm. per cent with albumin 4.8 gm. and globulin 1.5 gm. The patient was placed on an Aub diet for six days and during the last three days all the urine was collected and examined quantitatively for calcium. During this three day period, on an intake of 300 mg. of calcium, he excreted 1553 mg. of calcium, which was indicative of a strongly

negative calcium balance. Repeated blood analyses, this time done by Dr. Bodansky, disclosed calcium 13.6 mg. per 100 cc., phosphorus 1.9 and phosphatase 6.1 Bodansky units (normal values for adults are 2 to 3.5 units).

X-ray examination of the entire skeleton revealed only one significant finding. This was a small cyst in the neck of the right femur (fig. 1). There was a very slight generalized decalcification which was considered to be quite compatible with his age and not sufficient to warrant a diagnosis of hyperparathyroidism. An examination of the forearm and leg, made in comparison with another patient of the same age and weight, failed to show any definite evidence of decalcification. An x-ray examination of the oesophagus showed a pressure deformity on the right side, laterally and posteriorly, beginning about one inch beyond the junction of pharynx and oesophagus and corresponding to a mass about the size of a small lemon (fig. 2).

Urine examination showed a specific gravity of 1.012, a faint trace of albumin, and a few white blood cells. A urinary concentration test, in which five specimens were examined, revealed one with a specific gravity of 1.018; the other four varied from 1.014 to 1.016. Many



FIG. 1. X-ray of the right hip showing small cyst in the neck of the femur.

other urine examinations performed, both before and after operation, showed specific gravities ranging from 1.008 to 1.012 and usually a faint trace of albumin. The findings of the urinary sediment were not significant. A phenolsulfonphthalein test showed an excretion of only 33 per cent of the dye in four hours. The addition of Sulkowitch reagent to the urine caused a very heavy precipitate. X-ray examination of the urinary tract by means of intravenous urography failed to disclose any abnormalities. There were no calculi and no evidence of calcium deposits in the kidney parenchyma.

*Operation:* On June 21, 1944 the patient was operated on by Dr. J. Garlock who removed a "parathyroid adenoma, size of a tangerine, round, smooth, dusky reddish tan, located on right lower posterior capsule of thyroid."

*Surgical Pathology:* The specimen consisted of a plum-sized and shaped, well encapsulated tumor, reddish brown in color (fig. 3). On incision more than half of the tumor was found to be cystic. The remainder consisted of rather friable, reddish-brown tissue which was, in part, quite fleshy. Microscopic examination revealed typical parathyroid tissue composed of chief cells. Numerous cysts were present (fig. 4).

*Post-operative Course:* The post-operative course was remarkably smooth. The wound healed promptly and the patient was discharged at the end of one week, completely well.



FIG. 2. X-ray of the oesophagus showing pressure deformity produced by the parathyroid tumor.

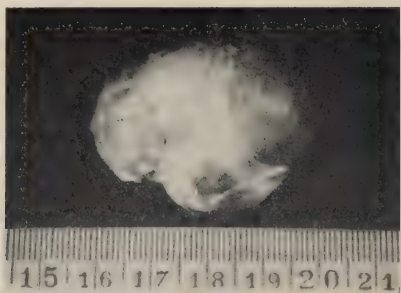


FIG. 3. Parathyroid adenoma, gross specimen.

He never manifested any signs of tetany. The blood calcium on the day after operation was 11.7 mg. per 100 cc., and the blood carbon dioxide 47.2 volumes per cent. Two days later the calcium was 10.1 mg. per 100 cc. and the carbon dioxide 55.5 volumes per cent. Post-operative medication consisted of the parenteral administration of 10 units of parathyroid extract one to three times a day, and the intravenous injection of one gram of calcium gluconate solution once or twice a day, for the first five days. He also received 10 gm. of calcium gluconate by mouth daily for the first week and 5 gm. daily for the second week. Two weeks after operation the blood calcium was 10.0 mg. per 100 cc.; there were no symptoms and the medication was stopped. The urine examined at first daily, and then at weekly intervals with the Sulkowitch reagent, showed a heavy precipitate until one month after the operation when the urine finally revealed only a faint precipitate.

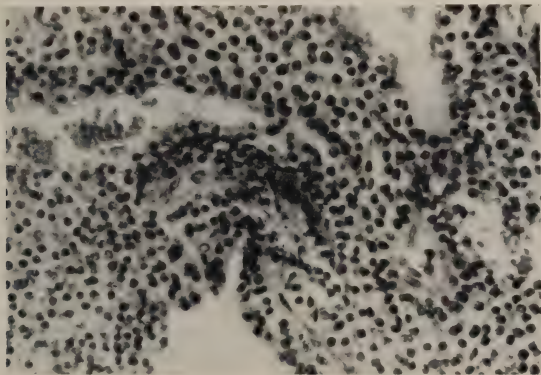


FIG. 4. Parathyroid adenoma. (Photomicrograph  $\times 500$ )

*Follow up:* The patient was re-examined on October 10, 1944, almost four months after the operation. The easy fatigability complained of originally, was less pronounced, but had not completely disappeared. His urinary frequency was less severe, occurring every two to three hours during the day and once at night. The blood pressure was 116 systolic and 74 diastolic. Examination of the blood revealed urea nitrogen 18.8 mg. per 100 cc., calcium 9.1 mg. and phosphorus 2.7 mg. The urine was crystal clear, had a specific gravity of 1.028, and contained no albumin or formed elements. A concentration test on the urine disclosed a specific gravity ranging from 1.026 to 1.028. A phenolsulfonphthalein test showed an excretion of 73 per cent of the dye in two hours. The Sulkowitch test on the urine revealed no precipitate. An x-ray examination of the pelvis and hip joints disclosed no change from the one taken before operation. There was no increased calcification and the small cyst in the right neck of the femur appeared unaltered.

#### DISCUSSION

It is perhaps unfortunate that the early cases of hyperparathyroidism were associated with Recklinghausen's disease. Our preoccupation with this rather rare, spectacular, disease may make us forget that the more prosaic renal calculus is sometimes a manifestation of this very same hyperparathyroidism. This

has been repeatedly stressed by certain investigators (6, 7), and reports from various clinics (8, 9) describe just such cases, discovered on routine investigation of purely urologic disorders. Only the realization that hyperparathyroidism can occur without any discernible bone changes, will permit diagnosis and treatment in the early stages of the disease before the occurrence of marked skeletal deformities and irreversible renal damage, which, although they may be arrested by removal of a parathyroid tumor, are apt to leave the patient permanently crippled. The diagnosis need not be too difficult. The simple procedure of adding Sulkowitch's reagent (12) to the urine of a patient with renal calculi may supply the clue to a possible hyperparathyroidism and determine the necessity for further investigation. This reagent, which consists of oxalic acid 2.5 gm., ammonium oxalate 2.5 gm., glacial acetic acid 5 cc. and distilled water up to 150 cc., when added to equal parts of acidified urine, causes a heavy, white precipitate in the presence of excessive calcium excretion in the urine. In normal urines there is usually a faint precipitate, although occasionally there may be none at all especially when the blood calcium is at the lower limits of normal or below. If the reaction is not strongly positive, the chances are much against the diagnosis of hyperparathyroidism. If, however, it is strongly positive, further investigation of the hypercalcinuria through the medium of appropriate blood chemical and, if necessary, calcium balance studies, is indicated. Further elaboration of the work-up will obviously depend on the findings obtained in these tests. It should be noted at this point that a strongly positive Sulkowitch reaction is not in itself a sign of hyperparathyroidism and should not be interpreted as such. It is merely an indication of hypercalcinuria which may be due to any number of causes. However, its occurrence in the presence of urolithiasis should make one suspicious enough of the possibility of hyperparathyroidism to warrant further investigation.

Cases of hyperparathyroidism with renal insufficiency have usually shown no improvement in renal function following removal of a parathyroid tumor (7, 13, 14). The report of a case by Snapper (11) disclosed some improvement, as indicated by the increased phenolsulfonphthalein excretion two years after operation, but even here there was evidence of residual renal impairment of moderate severity. Some advanced cases, which have shown an improvement in the skeletal manifestations after removal of a parathyroid tumor, have nevertheless progressed to a fatal termination due to renal failure.

Pathological examination of these kidneys, with their extensive fibrosis, calcification and destruction of vital renal tissue, clearly demonstrates why this renal process is usually irreversible, even though the inciting mechanism is removed. Therefore, the finding of early impairment of renal function in this case, with restitution to normal after surgical extirpation of a parathyroid adenoma, is of some interest. Although there was never any azotemia or hypertension, the deficient concentrating power of the kidneys and the low phenol-sulfonphthalein excretion offer fairly substantial proof of this contention. It is of interest to note in this connection, that cases with even more advanced renal insufficiency often exhibit no elevation of blood pressure and are apt to



show an albuminuria and abnormal findings in the urinary sediment which seem low in proportion to the degree of functional failure (16). From a consideration of the pathological process described above, it would seem fair to conclude that the reversibility of the renal damage in this case was due to the early stage of involvement at which therapy was instituted. Of course, the exact type of renal damage, existing at the time of the operation, is difficult to appraise and at best is more or less speculative in nature. It would seem safe to assume that the renal damage was not due to pyelonephritis, as there was never any clinical or laboratory evidence of urinary infection in this patient. Furthermore, examination of the urinary tract, just prior to operation, at which time the impaired renal function was evident, failed to disclose any signs of urolithiasis or infection. If we are to accept the concept of Albright and his co-workers that the earliest stage in the pathogenesis of the renal lesion in hyperparathyroidism is a precipitation of calcium phosphate crystals in the collecting tubules, and a subsequent "inflammation," it is possible to imagine a pathological process of this sort being responsible for the early renal damage in this case. A lesion of this type may well be reversible if the stimulus of increased parathyroid activity is removed before sclerosis, and ultimate contraction of the kidneys occur. Even if this conception is not true, the knowledge, that mild renal damage in this disease may be reversible, should serve as an additional spur to the early diagnosis and treatment of these cases.

#### SUMMARY

A case of hyperparathyroidism in which the signs and symptoms were almost entirely urologic in character is reported. Chemical examination revealed the typical picture of hypercalcemia, hypophosphatemia, hypercalcinuria, increased blood phosphatase and strongly negative calcium balance seen in this disease. At operation a large, cystic parathyroid adenoma, which had been suspected preoperatively, both clinically and roentgenographically, was found and removed. There was also early, but definite, renal impairment, unassociated with pyelonephritis. Four months after removal of the tumor the renal function was found to be normal.

#### BIBLIOGRAPHY

1. MANDL, F.: Klinisches und Experimentelles zur Frage der lokalisierten und generalisierten Ostitis fibrosa: B. Die generalisierte Form der Ostitis fibrosa. *Arch. f. Chir.*, 143: 245, 1926.
2. GOLD, E.: Ueber die Bedeutung der Epithelkörpervergrößerung bei der Ostitis fibrosa generalisata Recklinghausen, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 41: 63, 1928.
3. SNAPPER, I.: Parathyroid tumor and changes of the bones. *Arch. Int. Med.*, 46: 506, 1930.
4. BARR, D. P., BULGER, H. A., AND DIXON, H. H.: Hyperparathyroidism. *J. A. M. A.*, 92: 951, 1929.
5. WILDER, R. M.: Hyperparathyroidism: Tumor of the parathyroid glands associated with osteitis fibrosa. *Endocrinology*, 13: 231, 1929.

6. ALBRIGHT, F., AUB, J. C., AND BAUER, W.: Hyperparathyroidism. *J. A. M. A.*, 102: 1276, 1934.
7. ALBRIGHT, F., BAIRD, P. C., COPE, O., AND BLOOMBERG, E.: Renal complications of hyperparathyroidism. *Am. J. M. Sc.*, 187: 49, 1934.
8. BARNEY, J. D., AND MINTZ, E. R.: Relation of parathyroid glands to urinary lithiasis. *Brit. J. Urol.*, 8: 36, 1936.
9. CHUTE, R.: Clinical aspects of hyperparathyroidism with special reference to urology. *J. Urol.* 41: 762, 1939.
10. GRIFFEN, M., OSTERBERG, A. E., AND BRAASCH, W. F.: Blood calcium, phosphorus and phosphatase in urinary lithiasis, *J. A. M. A.* 111: 683, 1938.
11. SNAPPER, I.: *Medical Clinics on Bone Diseases*, New York, Interscience Publishers, Inc., 1943.
12. BARNEY, J. D., AND SULKOWITCH, H. W.: Progress in management of urinary calculi, *J. Urol.* 37: 746, 1937.
13. BELLIN, D. E., AND GERSHWIN, B. S.: Hyperparathyroidism with renal insufficiency. *Am. J. M. Sc.* 190: 519, 1935.
14. ELSON, K. A., WOOD, F. C., AND RAVDIN, I. S.: Hyperparathyroidism with renal insufficiency: Report of a case. *Am. J. M. Sc.*, 190: 49, 1936.

## EARLY CERVICAL CARCINOMA IN THREE CLINICALLY UNSUSPECTED CASES INCIDENTAL TO PLASTIC OPERATIONS\*

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The diagnosis of early cervical carcinoma has generally been made by routine histologic study of excised specimens. When the diagnosis of carcinoma is clinically ventured and proven by pathological section, the lesion is frequently pretty well established. Schottländer and Kermauner (1) for instance have met early uterine carcinoma in only 2 per cent of their large material and discovered it as an accidental finding in the routine laboratory examination of excised uterine specimens. Frankl (2) met early clinical uterine cancers in about 3 per cent of 1007 cases. Frank (3) writes that in his clinical experience of 30 years he has seen "but 2 cases of early cancer of the cervix in which a histological examination was really needed to confirm the diagnosis. In all other cases the clinical criteria were unmistakable."

The statistics are considerably different when biopsies are made from the vaginal portion of the cervix in suspected cases of carcinoma. Of 106 exploratory excisions reported from the second University Gynecological Clinic of Vienna in cases clinically suspected of cancer 46.2 per cent proved positive. One of these was an exceedingly young growth found in the amputated cervix from a case operated upon for uterine prolapse. This young carcinoma was included in my report of three cases of incipient cervical carcinoma from the same clinic (4).

Undoubtedly the vast majority of these lesions were sufficiently advanced to arouse suspicion of their malignancy. However, routine biopsies in all cases of cervical erosion may not be expected to yield so large a percentage of positive evidence of malignancy. In fact an unusually large number of such biopsies resulted in negative findings which is particularly true for women married to circumcised males. The apparent relative immunity of Jewish and Mohammedan women to cervical cancer is well known. H. N. Vineberg (5) estimated the comparative frequency to be 1 to 15 or 20 in women of other religious faiths and observances. This observation must be considered in estimating probable negative or positive results from biopsy examinations for cervical cancer. It accounts for the fact that since 1913 (6) only three additional cases presently to be reported have been encountered by me at The Mount Sinai Hospital.

TeLinde and Galvin (7) have very recently reported from the Johns Hopkins University and Hospital, eleven cases of early cervical cancer eight of which were encountered within a 12 month period. During this time 704 cervical biopsies were made, an incidence of 1.7 per cent which approximates that reported by Schottländer and Kermauner. TeLinde and Galvin properly suggest that some

\*I am indebted to Dr. Paul Klemperer for the pathological data and to Dr. S. Otani for the photomicrographs.

of these lesions may have been missed in former years. They believe that the greater recent incidence is due to a great increase in the number of biopsies taken in their Out-Patient Department and by their attending gynecologists in private practice.

In view of the universal agreement that the only practical solution to successful treatment of carcinoma is early detection it is necessary to report all such cases so that they may be better appreciated and recognized.

The present report deals with three cases of cervical carcinoma which were clinically unsuspected. The pathological diagnosis was however definite and made without reservation. One of these was incidental to a trachelorrhaphy; the other two were encountered in cervixes amputated as part of the technical procedure of the Fothergill operation. The clinical and pathological history including follow-up course are of sufficient interest to warrant putting them on record.

#### REPORT OF CASES

*Case 1. History:* B. L. (#11020), aged 48 years, gravida and para 4, was first seen March 7, 1936. Her chief complaint was frequent menstrual bleeding and a burning sensation in the vagina. Except for an appendectomy at 28 years she had been generally well. For the two previous months she had bled at two weekly intervals. Her uterus was slightly enlarged and presented a small hickory nut sized nodule on the anterior wall. The cervix was bilaterally lacerated and slightly eroded.

When next seen on August 8, 1936, she reported that she had bled three times in one month. The gynecological examination showed no essential change. On August 11, 1936, a dilatation and curettage with an Emmet trachelorrhaphy was done. At the operation it was noticed that the cervical erosion was slightly hypertrophic but it did not bleed on contact with fingers or sound. There was nothing grossly suspicious of carcinoma either in the curettings or in the removed cervical fragments. The pathological report was: (1) resting endometrium; (2) one small fragment showing infiltrating squamous cell carcinoma (medium ripe) (figs. 1 and 2).

The patient's husband was informed of the pathological diagnosis and of the urgent advisability of doing a hysterectomy or resorting to radiotherapy. He refused consent to either procedure saying his wife had cancerophobia and he did not wish to take the responsibility of urging her to carry out either recommendation.

August 27, 1936, the patient reported having hot flushes at night with frequent nervous spells. At this time the cervix was seen to be well healed.

September 9, 1937, the patient stated that her last previous menstrual period was in April 1937. The uterus was normal in size, the cervix looked normal. Returning to the office after an absence of nearly three years she reported January 12, 1940, that she had taken approximately 7,300,000 international units of menformon during the year. Amenorrhea for 6 months was followed by continuous and, at times, profuse bleeding of 3 weeks duration. During the two year period 1937 to 1939 she had bled about every third month. The cervix appeared normal.

March 8, 1940, there had been staining instead of menses in the past 3 months with irregular intervals of bleeding.

July 3, 1941, she reported still taking menformon till 5 days ago. There is slight staining. In view of the persistent bleeding the nature of which could not be determined in this case by any surgical procedure I took occasion on July 8, 1941, to inject visco rayopake into the uterus. The hystrogram showed a small but otherwise normal uterine cavity. Cessation of bleeding the same month was final.

November 23, 1943, examination showed the cervix to be unchanged, the uterus small and

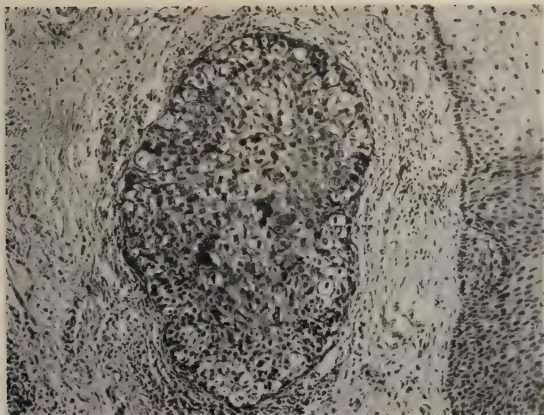


FIG. 1. Beneath the surface epithelium a nest of squamous epithelium with striking cell atypism and hyperchromatic nuclei.

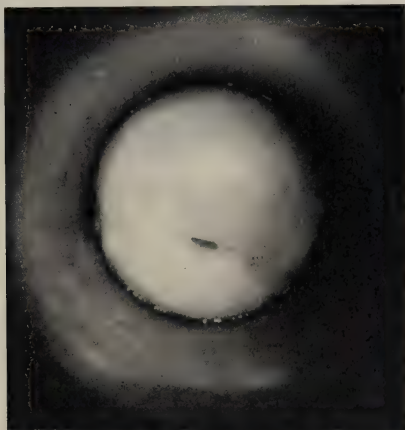


FIG. 2. Gross appearance of cervix showing no abnormalities.

freely movable; the adnexae were not palpable; the parametrial areas were free. As nearly as could be estimated this patient had taken a total of 9,100,000 international units of men-formon during a period of four years.



*Case 2. History:* R. C. (#450436), 55 years old, gravida 4, para 3; entered The Mount Sinai Hospital December 27, 1939. Her menses ceased 7 years ago. There has been no further bleeding. Her first two deliveries were difficult necessitating instrumentation. When menopause occurred 7 years ago she was told her womb was low but it caused no symptoms. In the past year she has noted protrusion while walking and moderate leucorrhea. No other symptoms were complained of.

Her physical condition was generally good. The blood pressure was 170 systolic and 106 diastolic. She had a relaxed parous introitus; a large cystocele with prolapse of cervix to the introitus. The cervix showed no conspicuous changes. There was a large rectocele. A Fothergill operation (parametrial fixation) was done December 28, 1939.

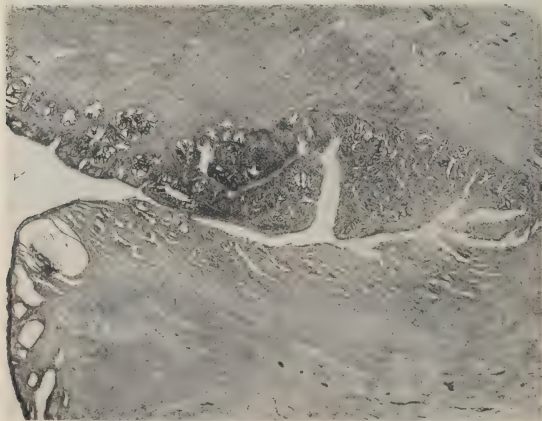


FIG. 3. Low power view of vaginal portion of cervix and canal. Anterior wall with regular and sparsely spaced cervical glands. Posterior wall showing conspicuous thickening of endocervix with marked glandular proliferation.

The pathological report of the amputated cervix was early adenocarcinoma (figs. 3, 4). Radiotherapy was advised and was instituted. This consisted of external radiation totaling 1200 R prior to re-admission in February of 1940, and again the same month she received 1800 mgm. hours of radium radiation, by tandem intracervically. The curettings of the cervical stump at that time showed fragments of cervical mucosa with acute inflammation and foreign body giant cells. No tumor was found.

The repair was unaffected and the anatomical result was good. On March 11, 1940, 1800 mgm. hours of intra-uterine radiation was again given. On June 13, 1940, examination showed the cervix to be clean but surrounded with a few small synechiae which were broken up. Three months later, the vagina was seen to be short and scarred and about  $1\frac{1}{2}$  inches long admitting one finger. Pruritus vulvae was present. The parametriae were free. December 20, 1940, synechiae were again noticed in the vault. September 27, 1941, biopsy of granulation tissue in the vaginal vault was reported as granulation tissue with acute and chronic inflammation. October 12, 1944, the patient was found to be well. A few nodules in the floor of the vagina, noted during the past 3 years, were still present.

*Case 3. History:* F. P. (#419794), aged 55 years, gravida 13, para 9, entered The Mount

Sinai Hospital February 3, 1938. It was her third admission to the hospital. She had previously been on the Medical Service because of hypertension and cardiac disease. She had her menopause at the age of 48 and had no vaginal bleeding since then. For the past year she had symptoms of a protrusion of a mass from the vagina, frequency, urgency and slight dysuria which became progressively worse.

Examination revealed an obese short female, not dyspneic or orthopneic. Examination of her lungs showed some emphysematous changes. The heart was enlarged to one finger-breadth to the left of the midclavicular line, the sounds were of fair quality; her blood pressure was 170 systolic and 100 diastolic.

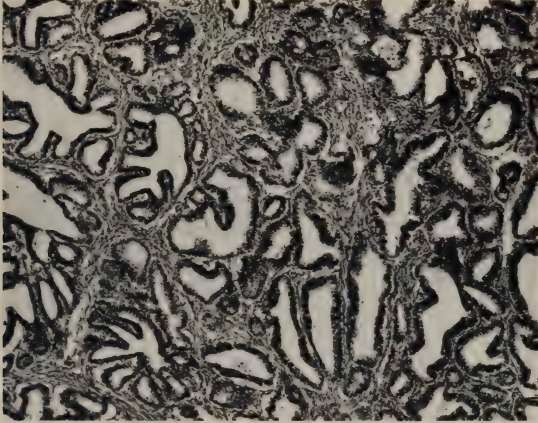


FIG. 4. High power of thickened endocervix showing closely approximated branching glands with multilayer densely packed cells with hyperchromatic nuclei.

She had a multiparous relaxed introitus with a large billiard-ball cystocele and a moderate-sized rectocele. The cervix descended to the introitus on straining; it was lacerated and slightly eroded. The uterus was small, freely movable, retrocessed. The adnexae were not palpable.

February 5, 1938, an anterior and posterior colporrhaphy with Fothergill parametrial fixation operation was performed. During the preliminary dilatation for the routine curettage it was felt that the lower portion of the anterior uterine wall was possibly perforated during the cervical dilatation with the Goodall dilator therefore no curettage was performed. The plastic procedure however was carried out.

Pathological report of the amputated cervix was chronic endocervicitis with early endocervical squamous cell carcinoma (fig. 5).

Her convalescence was uneventful except for a rise in temperature to 102°F. on the first postoperative day. It was normal the 3rd day after which it remained normal until her discharge from the hospital on the 21st postoperative day. Previous to her discharge she was given 7 x-ray treatments to the pelvis and was referred to the Radiotherapy Department for further treatment.

Final note at the time of discharge: "Cervix stays well up on straining. The anterior and posterior vaginal walls do not descend."

On June 17, 1943, the patient was again admitted having noted vaginal spotting for one month. A small endocervical erosion was seen which bled easily. A hystero-gram at this time showed the uterine cavity to be enlarged and markedly irregular, with evidence of a mass projecting upwards from the left inferior surface. (X-ray #43400) Pathological report: Cervical biopsy showed fragments of tissue with infiltrating squamous cell carcinoma of the mature type. There was a profuse discharge of foul green pus from the uterus at the time of insertion of radium on July 8, 1943, after which she received 7200 mgm. hours by tandem and colpostat. On September 20, 1943 at the radiotherapy follow-up she reported pain in the region of the left vulva. The cervix was healed and pulled to the right by the shortened right parametrium. Clinically there was no evidence of disease. On October 14, 1943, the patient received the final x-ray treatment which totalled 2800 R units.

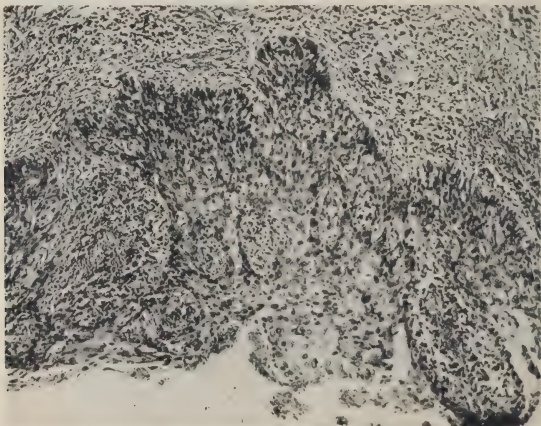


FIG. 5. Surface epithelium of cervix with striking cell atypism and immature squamous epithelial cells invading the stroma.

#### COMMENT

The question of malignancy in the early lesions just described recurs despite accumulating experience of the last 30 years and more. Of the three cases herein reported the later finding of carcinoma in the cervical stump of one of the two cases where a Fothergill operation was done leaves no doubt as to the malignancy. The case where a trachelorrhaphy was done showing so far no metastasis or local recurrence and the other case incidental to the Fothergill operation also without evidence of recurrence leave room for theoretical speculation on two points. (1) Was the lesion truly cancerous and if so was it relatively latent or (2) may one assume that the cancer can be totally removed provided it is small enough.

In 1910 (4) I reported three cases of incipient carcinoma of the cervix which

were encountered in cervixes two of which were removed for the relief of prolapse and the third was removed with a myomatous uterus. The lesions were unsuspected and were discovered in the course of the routine histologic examination. In 1913 two more cases were added. The criteria by which carcinoma was determined were previously published by Shottländer, (8) Sitzenfrey (9), Pronai (10), and later by Ewing (11) and by Rubin (4) on purely morphological grounds. There was no follow-up of these cases. A number of pathologists, notably L. Pick, questioned the validity of these criteria. The cell changes which were presumed to be characteristic of early carcinoma are the following:

1. A well-marked atypical condition of epithelium which is converted from a single cylindrical to a metaplastic many-layered variety.
2. A well-marked difference in size of the individual cells in their shape, arrangement and chromatin content.
3. The presence of atypical mitosis.
4. The presence of giant nuclei or of giant cells.

Isolated alveoli and penetration into the depth of such epithelium may be present at this early stage, but this is not to be regarded as an essential characteristic of malignancy. These are rather the later developments of an advanced carcinoma with its other signs of cornification, ulceration, etc.

In 1921 T. S. Cullen (12) reported an early case of cervical carcinoma which corresponded in practically all respects to the cases reported above. Cullen's case was that of a woman 45 years old, a nulligravida who was curetted for menometrorrhagia. In addition to the hyperplastic endometrium found in the curettings there was a small area showing squamous cell carcinoma. A second curettage yielded the earliest evidence of the formation of squamous cell carcinoma Cullen had ever seen. A small submucous myoma was present in the fundus of the removed uterus. The finding of the carcinoma was regarded by Cullen "as one of those fortunate coincidences that will occasionally occur where the routine microscopic examination of scrapings is undertaken."

Schottländer's summary of the three possibilities of early diagnosis in uterine cancer may be recalled:

1. The material examined reveals a benign lesion as determined by the morphological character of the epithelial areas and foci in question, even though there is an indication of beginning deeper penetration. The epithelium is normal or shows healing erosion or a so-called metaplastic epithelium of the uterine cavity.
2. There is a group of cases in which we are unable to determine whether the alteration in the epithelium indicates a benign or a malignant change. These patients should not be operated upon at once, but should be controlled by frequent and repeated subsequent examinations.
3. Finally, it is possible to recognize small cancer foci owing to a well-marked morphological cell-aberration even though the deep penetration of epithelial sprouts is barely present or altogether absent.

This classification has a direct practical bearing. The borderline cases, where the pathologist cannot positively make up his mind as to the benign or



malignant nature of the lesion, necessitate further vigilance over the patient. A second biopsy or diagnostic curettage may be resorted to in these doubtful cases.

Benign metaplasia of the cervical or uterine epithelium formerly regarded as precancerous should no longer be mistaken for cancer. Much was said in the early decade of the present century on the subject of certain proliferations of the surface epithelium especially those found associated with the healing of cervical erosions as to whether they were benign or potentially malignant, i.e., precancerous. It seems unprofitable to speculate as to whether a lesion is potentially cancerous because only time can tell. On the other hand if there are outspoken characteristics of cancer no matter how small the lesion may be the treatment should be unequivocally radical, that is by total hysterectomy or radiation therapy.

The morphological cellular changes in epithelium characterizing cancer have since been substantiated by Robert Meyer (13), W. Schiller (14), H. Hinselmann (15) and others. Further proof was adduced from the subsequent course of such cases which developed undoubted recurrences or metastases. The lesions encountered in these early cases are very small, at times no bigger than a pinhead but they show microscopically all the characters of a cancerous lesion. In this connection it is worthwhile noting Robert Meyer's (13) opinion: "It is necessary to arrive at a diagnosis at the earliest possible moment in the natural history of the cancer process. Microscopic changes in the cells are the earliest which can be recognized, and these can be accepted as trustworthy before invasion. Adenocarcinoma of the body of the uterus is diagnosed by every pathologist from curettings which consist only of superficial tissue. The changed tissue form and structure are sufficient without evidence of invasion."

The histological characteristics of early carcinoma are now thoroughly familiar to all well trained pathologists. TeLinde's and Galvin's cases have offered the most recent corroboration of these diagnostic criteria and of the minimal histological changes which justify a diagnosis of cervical carcinoma. In none of their eleven cases was a diagnosis possible from palpation or inspection of the cervix.

The absence of recurrence in Case I of the present report despite massive estrogen therapy suggests a certain degree of latency of some early lesions. Nevertheless, it would be hazardous with the present limited knowledge of this type of early cancer to advocate minor procedures as adequate therapy instead of resorting to radiotherapy or total hysterectomy. Although seven years have elapsed since the trachelorrhaphy it is not certain whether further growth may not eventually become manifest. Late recurrences have been met many years after radical removal of a cancer. The growth potential in this case does not appear to be great. Its latency however is unpredictable.

TeLinde and Galvin mention a similar case in which a trachelorrhaphy was done in June 1919. Routine examination of tissue removed showed non-invasive changes in surface epithelium similar to those seen in the present series. Eight and one-half years later examination of this patient showed a large cauli-



flower-like carcinoma of the cervix. In another case the biopsy showed non-invasive carcinoma-like change but the cervix which was removed postmortem three years later exhibited extensive changes in the surface epithelium with invasion into the stroma of the cervix at many points.

#### SUMMARY

Three cases of early cancer of the cervix are reported. One was discovered in small cervical fragments removed during a trachelorrhaphy. This patient was followed for 7 years; there was no evidence of recurrence or further growth. Of the two remaining cases, both of which were incidental to Fothergill operations, the lesion being discovered in the amputated cervix, one developed recurrence in the cervical stump 5 years and 4 months after the operation despite ample x-ray and radium therapy. The other also treated has so far (5 years after operation) shown no recurrence. The question of latency of these early cancers and the morphologic criteria of early cancer is discussed.

#### REFERENCES

1. SCHOTTLÄNDER, J., AND KERMAUNER, F.: Uterus Karzinom. Berlin, S. Karger, 1912.
2. FRANKL, O.: Monatschr. f. Geburtsh. u. Gynäk., 48: 178, 1918.
3. FRANK, R. T.: Gynecological and Obstetrical Pathology. New York, D. Appleton & Co., 1931.
4. RUBIN, I. C.: The pathological diagnosis of incipient carcinoma of the uterus. Am. J. Obst. & Gynec., 62: 4, 1910.
5. VINEBERG, H. N.: The Relative Infrequency of Cancer of the Uterus in Women of the Hebrew Race. Anniversary Volume dedicated to Sir William Osler, July, 1919.
6. RUBIN, I. C.: The early diagnosis of uterine cancer. Am. J. Surg., 1913.
7. TELINDE, RICHARD W., AND GALVIN, GERALD: The Minimal Histological Changes in Biopsies to Justify a Diagnosis of Cervical Cancer. Paper presented at the American Gynecological Society, June, 1944.
8. SCHOTTLÄNDER, J.: Gynäk. Rundschau, p. 509, 1912.
9. SITZENFREY, A.: Ztschr. f. Geburtsh. in Gynäk., Bd. 59, 1907.
10. PRONAI, K.: Arch. f. Gynäk. Bd. 89, p. 596.
11. EWING, J.: Early diagnosis of cancer. M. Rec., 1914.
12. CULLEN, T. S.: Early Squamous-Cell Carcinoma of the Cervix. Surg., Gynec. & Obst., 33: 137, 1921.
13. MEYER, R.: The basis of the histological diagnosis of carcinoma. With special reference to carcinoma of the cervix and similar lesions. Surg., Gynec. & Obst., 73: 14, 1941.
14. SCHILLER, W.: Early diagnosis of cancer of the cervix. Surg., Gynec. & Obst., 56: 210, 1933.
15. HINSELMANN, H.: Etiology, symptomatology and diagnosis of uterine cancer. Veit. Stoeckel, 6: 1, 854, 1930.  
Colposcopy. Davis: Gynec. & Obst., Volume 3, 1934.

# PLASMA CELL INVASION OF PERIPHERAL BLOOD IN MULTIPLE MYELOMA

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The occurrence of plasma cells in the peripheral blood in cases of multiple myeloma has been the subject of several reports. These cases are chiefly interesting because of two considerations: (1) the importance of the examination of the blood in the diagnosis of multiple myeloma and (2) the status of plasma cell leukemia and its relation to myeloma.

The possibility of the passage of myeloma cells from the bone marrow into the peripheral circulation has not been universally acknowledged. Some authors question the existence of characteristic myeloma cells in the blood. However, there are many cases reported as multiple myeloma in which plasma cells were found in the peripheral blood.

It has been stated that two types of plasma cells may be found in the circulating blood, the "typical" and the "atypical." The typical plasma cell as described by Marschalkó (1) has little significance in the diagnosis of myeloma, as it may be seen in other unrelated conditions (rubella, infectious mononucleosis, etc.) Morissette and Watkins (2) have stressed the importance of atypical plasma cells when found in blood smears. They give the following morphological characteristics for the differentiation of the two types: The typical plasma cell is characterized by a small "Redkern" eccentric nucleus, light staining perinuclear "Hof," and basophilic cytoplasm; the myeloma cells, however, are usually larger (up to 25 $\mu$  in diameter), have a large nucleus which is rather centrally placed and devoid of perinuclear "Hof"; the nuclear pattern shows a sharp demarkation between the chromatin and parachromatin substance. Moreover, in the atypical plasma cell there is at least one nucleolus, and the basophilic cytoplasm shows more tendency to vacuolization than is seen in the typical plasma cells. The authors believe that these atypical plasma cells, if carefully looked for, may be found in more cases of myeloma than is generally recognized. They also state that all the intermediaries between the typical and atypical plasma cells may be seen in blood smears. The greater the resemblance of the cells found in the blood to the atypical forms of plasma cells, the greater will be the likelihood of the diagnosis of myeloma.

Rosenthal and Vogel (3) stress the following characteristics of plasma myeloma cells in distinguishing them from plasma cells in such conditions as serum disease, infectious mononucleosis and in inflammatory areas: "They are much larger in size; the cytoplasm is considerably greater, does not assume the deep basophilic staining quality with the Giemsa stain and does not show the characteristic

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Part of the clinical and laboratory studies were performed at the Montefiore Hospital.

stain with Pappenheim's methyl—green pyronin. The myeloma cells show the characteristics of myeloid cells, whereas the genuine plasma cells resemble the lymphocytes. The oxidase reaction is negative in plasma cells, but is present in the granular cells of myelocytic myeloma. In supravital preparations, the plasma cells show an eccentric nucleus and a clear homogeneous cytoplasm. Large dense mitochondria appear around the nucleus."

The failure to differentiate between these types of plasma cells is one of the chief causes of disagreement concerning plasma cell leukemia. This disagreement is illustrated by the following example: The first case reported as plasma cell leukemia was that of Foà (4) in 1902. Osgood and Hunter (5) reported their case (1935) as the second in the literature, while Patek and Castle (6) two years later described another instance and cited eleven others that had been previously reported. The authors differ widely as to the cases which they accept as plasma cell leukemia. This discrepancy is also explained by the fact that the distinction between the localized and the diffuse forms of plasma cell infiltration is not sharp. Therefore all attempted classifications of these conditions, such as that of Piney and Riah (7), must be to some extent arbitrary.

The views expressed by Reiter and Freeman (8) are noteworthy. The authors report a case in which all the organs, as well as the blood, were diffusely involved, a condition which they term leukemic plasmocytosis. They discuss the relationship of this condition to localized myeloma and draw an analogy with the proliferative diseases of the lymphocytes. The authors contend that plasma cell multiple myeloma is analogous to lymphosarcoma. Invasion of the peripheral blood does not occur in either condition. On the other hand, plasma-cell leukemia is comparable to true lymphatic leukemia. Between these two extremes, involving either the plasma cell or the lymphocyte, is a group in which tumor formation and blood invasion is combined. The name "leukosarcoma" is applied to those cases in which the lymphocytes are involved; they suggest the term "leukemic plasmacytosis" for cases involving plasma cells. These latter cases of plasma cell myeloma with plasmocytosis differ from plasma cell leukemia as leukosarcoma differs from lymphatic leukemia.

In general, two concepts have been advanced to explain the significance of plasmocytosis in multiple myeloma; (1) that of a true leukemia, and (2) of a plasmocytic reaction in the blood (analogous to a leukemoid reaction) caused by tumors which are essentially localized in nature (9).

The most important data concerning cases reported in the literature as plasma cell leukemia (either pure or associated with localized myeloma) are compiled in Table I.

The following case of multiple myeloma is reported because the examination of the peripheral blood disclosed atypical plasma cells which suggested the diagnosis before other tests were performed. Subsequently the blood picture of plasma cell leukemia developed.

#### CASE REPORT

*History:* The patient was a 58 year old woman, first seen on August 6, 1943, complaining of abdominal and low back pain and pain on swallowing. Because of the occurrence of "albuminuria" the diagnosis of kidney disease had been entertained.

TABLE I  
Cases of plasma cell leukemia reported in the literature

| AUTHOR                                     | AGE | SEX | SYMPTOMS;<br>DURATION                                  | PHYSICAL FINDINGS<br>X-RAY  | URINE                               | HEMO-<br>GLOBIN           | BLOOD                |                                    |                 |          | TOTAL<br>PRO-<br>TEIN | GLOBULIN | AUTOPSY FINDINGS  |
|--|-----|-----|--|---|-------------------------------------|---------------------------|----------------------|------------------------------------|-----------------|----------|-----------------------|----------|---|
|  |     |     |  |   |                                     |                           | Red<br>Cell<br>Count | White<br>Cell<br>Count             | Plasma<br>Cells | %        |                       |          |   |
| Gluzinski and<br>Reichenstein<br>(10) 1906 | 46  | M   | Chest pain;<br>bleeding<br>gums<br>1 year              | Tumors of ribs and<br>sternum; spleno-<br>megaly and general<br>lymphadenopathy | Albumose                            | I) 55%<br>II) 15%         |                      | 7,600                              |                 | 72       | %                     |          | Diffuse plasma cell in-<br>filtration of bone<br>marrow and spleen                    |
| Ghon and<br>Roman (11)<br>1913             | 72  | F   | Abdominal<br>pain; nodes<br>in the neck<br>Few weeks   | Splenomegato-<br>megaly; lymphad-<br>enopathy                                   | Negative                            | 9.56 Gm.<br>in 100<br>cc. |                      | 13,000                             |                 | 1        |                       |          | Diffuse plasma cell in-<br>filtration of bone mar-<br>row, lungs, kidney,<br>pancreas |
| Ghon and<br>Roman (11)<br>1913             | 53  | M   | Mouth gan-<br>grene bleed-<br>ing gums<br>Few weeks    | Splenomegato-<br>megaly; lymphad-<br>enopathy                                   | Negative                            |                           | 2.5m                 | 6,200                              |                 | 15       |                       |          | Plasma cell infiltration<br>of bone marrow,<br>spleen, liver, lymph<br>nodes          |
| Muller and<br>McNaughton<br>(12) 1931      | 38  | F   | Bone and mus-<br>cle pain;<br>2 years                  | Splenomegato-<br>megaly; lymphad-<br>enopathy                                   | Negative                            | I) 75%<br>II) 41%         |                      | 11) (3 mos. later)<br>27,000       |                 | 46       |                       |          | Plasma cell infiltration<br>of bone marrow,<br>spleen, liver, kidney,<br>lymph nodes  |
| Muller and<br>McNaughton<br>(12) 1931      | 46  | F   | Backache<br>Few months                                 | Punched-out lesions<br>in the x-ray films<br>of skull and verte-<br>brae        | Bence-<br>Jones<br>Protein-<br>uria |                           |                      | 60,000                             |                 | 65       |                       |          |   |
| Piney and Riach<br>(8) 1932                | 56  | M   | Frontal tumor<br>Subcutane-<br>ous nodules<br>6 months |   |                                     | I) 47%<br>II) 11)         |                      | 23,000<br>(1 week later)<br>42,000 |                 | 16<br>33 |                       |          | Plasma cell infiltration<br>of bone marrow and<br>almost all viscera                  |

|                                 |    |   |  |                                       |                              |  |                  |          |    |      |      |   |
|---------------------------------|----|---|--|---------------------------------------|------------------------------|--|------------------|----------|----|------|------|---|
| Piney (13) 1932                 | 48 | M | Backache   | Splenomegaly;<br>lymphadenopathy      | Albumin-<br>uria             |  |                  | 20 000   | 41 |      |      | Diffuse plasma cell infiltration of bone marrow, spleen, lymph nodes                    |
| Osgood and Hunter (5) 1934      | 49 | M | Nose bleeds;<br>General weakness;<br>6 months        | Axillary and inguinal lymphadenopathy | Negative                     | I) 30%<br>II) (2 days later)<br>34 000 | 16 000           |          |    | 8.79 | 6.94 | Diffuse plasma cell infiltration of bone marrow, spleen, lymph glands                   |
| Patek and Castle (6) 1936       | 60 | F | Backache;<br>bleeding                                |                                       | Bence-Jones Protein-<br>uria | I)<br>II)                              | 21 000<br>50 000 | 24<br>33 |    | 11.9 | 8.8  | Diffuse plasma cell infiltration of bone marrow, spleen, lymph glands, kidney pancreas. |
| Fleishacker and Klima (14) 1936 | 62 | M | Loss of wt.;<br>weakness<br>6 months                 | Splenohepatomegaly                    |                              | 15%                                    | 14 000           | 23       |    |      |      | Diffuse plasma cell infiltration of bone marrow, spleen, lymph glands, kidney, pancreas |
| Fleishacker and Klima (14) 1936 | 46 | M | Pain in upper right quadrant. Nose bleeds<br>4 weeks | Splenohepatomegaly; Purpura           |                              | 35%                                    | 10 000           | 13       |    |      |      | Diffuse plasma cell infiltration of bone marrow, spleen, lymph glands, kidney, pancreas |
| Reiter and Freeman (8) 1938     | 66 | F | Pain in the arm; weakness<br>6 months                |                                       | Negative                     | 95%                                    | 1 000            | 49       |    |      |      | Diffuse plasma cell infiltration of bone marrow, spleen, lymph glands, kidney, pancreas |



TABLE I—Continued

| AUTHOR  | AGE | SEX | SYMPTOMS;<br>DURATION              | PHYSICAL FINDINGS<br>X-RAY  | URINE                      | HEMO-<br>GLOBIN                 | BLOOD                |                        |                 |   | TOTAL<br>PRO-<br>TEIN<br>% | GLOBULIN<br>% | Autopsy Findings  |
|---|-----|-----|------------------------------------|---|----------------------------|---------------------------------|----------------------|------------------------|-----------------|---|----------------------------|---------------|---|
|   |     |     |                                    |   |                            |                                 | Red<br>Cell<br>Count | White<br>Cell<br>Count | Plasma<br>Cells | % |                            |               |   |
| Schilling and<br>Wahlenberg<br>(16) 1938      |     |     | Bone pains;<br>Few years           | Punched-Out lesions<br>in the vertebrae—<br>(x-ray finding)   | Negative                   |                                 | 13,300               | 83                     |                 |   |                            |               | Diffuse plasma cell infiltration of bone marrow, spleen, lymph glands, kidney, pancreas |
| Lachnit and<br>Walterskircher<br>(16) 1939    | 60  | F   | Bleeding<br>tendency               | Hepatosplenomegaly  | Hematuria<br>Albuminuria   | 1) 64%<br>11) (four days later) | 10,000<br>11,500     | 53<br>71               |                 |   |                            |               | Plasma cell infiltration of bone marrow, liver, spleen, kidney                          |
| Askanaazy and<br>Dubois-Ferriere (17)<br>1942 | 76  | M   | Bone pains,<br>Backache<br>5 years | Diffuse osteoporosis<br>in bone x-ray   | Albuminuria<br>Proteinuria | 65%                             | 7,600                | 74                     | 11.05           |   |                            |               | Plasma cell infiltration in bone marrow   |
| Rubin (18) 1942                               | 35  | F   | Backache;<br>3 months              | Tenderness of the<br>lower spine; destructive lesions in<br>the vertebrae, ribs,<br>ilium               | Albuminuria                |                                 | 40,000               | 54                     |                 |   |                            |               | Biopsy of the bone lesions: plasma cell multiple myeloma                                |
| Rubin (18) 1942                               | 31  | M   | Fractured<br>clavicle<br>6 months  | Pulsating masses<br>over clavicle, ribs,<br>sternum, destructive lesions in almost all bones<br>(x-ray) |                            |                                 | 19,000               | 2                      |                 |   |                            |               | Biopsy of the bone lesions: plasma cell multiple myeloma                                |

She was well until two and a half years before, when she had a sudden, profuse, rectal hemorrhage requiring several blood transfusions. The cause of this bleeding could not be ascertained despite detailed examination. A platelet count was not done. From this period on she observed progressive weakness and pallor. Two months ago, low back pain, radiating to the buttock, appeared. Within a short time she became incapacitated.

TABLE II  
*Peripheral blood studies*

| DATE | HEMO-<br>GLOBIN<br>(SAHLI) | RED CELL<br>COUNT              | WHITE<br>CELL<br>COUNT | PLATELET<br>COUNT | DIFFERENTIAL COUNT                     |                                |                |                       |                   |                 |                 |
|------|----------------------------|--------------------------------|------------------------|-------------------|--|--------------------------------|----------------|-----------------------|-------------------|-----------------|-----------------|
|      |                            |                                |                        |                   | Non-<br>segmented<br>neutro-<br>philes | Segmented<br>neutro-<br>philes | Mono-<br>cytes | Lym-<br>pho-<br>cytes | Eosino-<br>philes | Baso-<br>philes | Plasma<br>cells |
|      | %                          | In mil-<br>lions per<br>1 cmm. | Per 1<br>cmm.          | Per 0<br>cmm.     | %                                      | %                              | %              | %                     | %                 | %               | %               |
| 7/6  | 31                         | 1,900                          | 6,000                  | 90,000            | 5                                      | 45                             | 6              | 41.5                  | 1                 | 1               | 0.5             |
| 8/20 | 48                         | 2,800                          | 6,400                  | 70,000            | 3                                      | 56                             | 4              | 31                    | 2                 | —               | 2               |
| 9/17 | 43                         | 2,620                          | 6,850                  | —                 | 2                                      | 47                             | 8              | 38                    | 2                 | —               | 2               |
| 9/22 | —                          | —                              | 15,000                 | —                 | 8                                      | 42                             | 7              | 22                    | 1                 | 1               | 19              |
| 9/24 | —                          | —                              | 17,400                 | —                 | 8                                      | 37                             | 4              | 23                    | 2                 | —               | 28              |
| 9/27 | 38                         | —                              | 26,000                 | —                 | 10                                     | 28                             | 6              | 17                    | 1                 | —               | 38              |

TABLE III  
*Bone Marrow Studies (Sternal Aspiration)*

| DATE.....                       | 7/6             | 8/20            | 9/27            |
|---------------------------------|-----------------|-----------------|-----------------|
| Total Nucleated Cell Count..... | 240,000         |                 |                 |
| Megakaryocytes per 1 cmm.....   | 22              |                 |                 |
|                                 | <i>per cent</i> | <i>per cent</i> | <i>per cent</i> |
| Differential Count              |                 |                 |                 |
| Myeloblasts.....                | 1               | 1.25            | —               |
| Promyelocytes.....              | 1               | 2.25            | 0.25            |
| Myelocytes Neutrophilic.....    | 8               | 10.25           | 5.75            |
| Myelocytes Eosinophilic.....    | 2               | 1               | —               |
| Non-Segmented Neutrophilic..... | 15              | 6               | 8.5             |
| Segmented Neutrophilic.....     | 2.3             | 3.25            | 4.25            |
| Segmented Eosinophiles.....     | 0.3             | 0.5             | 0.25            |
| Hematogones.....                | 0.3             | —               | 1.5             |
| Reticulum Cells.....            | 0.3             | —               | 0.5             |
| Erythroblasts.....              | 2               | 2.25            | 2               |
| Normoblasts.....                | 10.3            | 7.25            | 8.25            |
| Plasma Cells.....               | 56.6            | 66              | 68.5            |

*Examination:* The patient was a moderately obese and chronically ill woman. There were several small, soft, bright red nodules, measuring up to 7 mm. in diameter, scattered over the posterior third of the margins of the tongue. The anterior and posterior cervical lymph nodes, left axillary, left epitrochlear nodes, and inguinal nodes were palpable. The blood pressure was 185 systolic, 90 diastolic. The liver was felt 2 cm. below the costal margin. The abdomen was markedly distended; the spleen was not palpable. There was tenderness over spinous processes of L4 and L5 and the upper sacrum. In addition, marked tenderness was present over the left heel.

*Laboratory Data:* The blood count showed a very pronounced anemia of the hypochromic type: hemoglobin, 31 per cent; red blood cells, 1,900,000; white blood cells, 6,100. The differential count was normal except for an occasional atypical plasma cell, which contained one or more nucleoli; some showed mitotic figures or double nuclei; the cells were large and nuclei centrally situated. The possibility of plasma cell multiple myeloma was at once suggested by this appearance of the plasma cells. Sternal marrow aspiration confirmed the diagnosis of myeloma, revealing 56 per cent plasma myeloma cells; other elements were markedly reduced. The blood and bone marrow findings are described in Tables II and III.

Other blood studies were: urea nitrogen, 64 per cent; phosphorus, 5 mg. per cent; calcium, 10.4 mg. per cent; total protein, 7.3 gm. per cent; globulin, 4.4 gm. per cent; alkaline phosphatase 4 King-Armstrong units; sedimentation rate, 18 mm. in 8 minutes; and Wassermann reaction negative. The urea clearance was 11 per cent. The blood serum showed an immediate positive formol gel reaction. Using the ordinary heat test at pH 5 the urine was found to contain large quantities of Bence-Jones proteose and to be consistently free of albumin. There were occasional hyalin and granular casts. Urinary concentration tests showed a specific gravity of 1.012 to 1.015. Roentgenographic examination of the skull showed numerous circular lesions throughout the bones of the calvarium. There were numerous areas of bone destruction of the lower ribs, lumbar vertebrae, and pelvis and a pathological fracture of the body of the first sacral vertebra. Lumbar puncture showed evidence of spinal cord compression. The spinal fluid protein was 26 mg. per cent; the Pandy was four plus.

*Course:* During her stay in the Hospital, the patient had considerable back pain; radiotherapy brought no relief. She received several blood transfusions. The course was progressively downhill and she died on October 1, 1943. A post mortem examination was not obtained.

#### COMMENT

The most interesting findings observed in this case of multiple myeloma were in the blood picture. There was a progressive increase (absolute and relative) of the plasma cells coincident with a rise of the total white cell count and a fall of the neutrophiles.

The bone marrow was very cellular with an overwhelming preponderance of plasma myeloma cells. This was so pronounced as to crowd out the normal marrow elements. As a result, a severe anemia with thrombocytopenia ensued. It is possible that with increasing infiltration of the bone marrow, the plasma cells had succeeded in escaping into the peripheral blood.

Although no post-mortem examination was obtained, there was evidence of visceral extraosseous involvement. It was mentioned that the patient complained of pain in the back of her tongue; multiple nodules were found in this area. Aspiration of these nodules revealed 62 per cent plasma cells, whereas at that time, there were only 12 per cent plasma cells in the peripheral blood. The nodules represented foci of myelomatous tissue.

In retrospect, it is probable that the initial symptom of rectal bleeding is due to thrombocytopenia conditioned by plasma cell infiltration of the bone marrow. Complete hematologic studies are indicated in cases of unexplained bleeding. The earlier diagnosis of "albuminuria" is a common error. It stresses the importance of careful urine analyses. The reduction in kidney function and azotemia may be ascribed to a "myeloma kidney."

This case emphasizes the relationship between plasma cell leukemia and

multiple myeloma. It shows the importance of the examination of the blood smear in the diagnosis of myeloma. It is possible that the study of the morphology of the white cell layer of centrifuged blood may facilitate the discovery of plasma cells in more cases of multiple myeloma.

## SUMMARY

A case of multiple myeloma is presented in which the diagnosis was first suggested by the presence of plasma cells in the routine blood smear examination. The diagnosis was confirmed by bone marrow studies which showed similar plasma cells. Subsequently massive plasma cell invasion of the peripheral blood occurred. This resulted in the picture of plasma cell leukemia.

The relationship of plasma cell leukemia to multiple myeloma is discussed.

## REFERENCES

1. MARSCHALKE: quoted in Askanazy and Dubois-Ferriere (17).
2. MORISETTE, L., AND WATKINS, C. H.: Multiple myeloma: diagnostic value of the blood smear. *Proc. Staff Meet., Mayo Clin.*, 17: 433, 1942.
3. ROSENTHAL, N., AND VOGEL, P.: Value of sternal puncture in diagnosis of multiple myeloma. *J. Mt. Sinai Hosp.*, 4: 100, 1938.
4. FOA: quoted in Reiter and Freeman (8).
5. OSGOOD, E. E., AND HUNTER, W. C.: Plasma cell leukemia. *Folia haemat.*, 52: 369, 1934.
6. PATEK, A. J., AND CASTLE, W. B.: Plasma cell leukemia. *Am. J. M. Sci.*, 191: 788, 1936.
7. PINEY, A., AND RIAH, J. S.: Multiple myeloma, aleukemic and leukemic. *Folia haemat.*, 46: 37, 1937.
8. REITER, B. R., AND FREEMAN, J. T.: Plasma cell leukemia. *Am. J. M. Sci.*, 193: 38, 1937.
9. FLEISCHACKER, H.: Über die Bedeutung der Reticuloendothelien und Plasmazellen des Knochenmarkes, *Ergebn. d. inn. Med. u. Kinderh.*, 60: 508, 1941.
10. GLUZINSKI, A., AND REICHENSTEIN, M.: Myeloma and Leucemia lymphatica plasmacellularis, *Wien. klin. Wchnschr.*, 19: 336, 1906.
11. GHON, A., AND ROMAN, B.: Über pseudoleukemische und leukemische Plasmazellen-Hyperplasie, *Folia haemat.*, 15: 72, 1913.
12. MULLER, G., AND McNAUGHTON, E.: Multiple myeloma with blood picture of plasma cell leukemia, *Folia haemat.*, 46: 17, 1931.
13. PINEY, A.: Plasma cell leukemia, *Folia haemat.*, 30: 173, 1924.
14. FLEISCHACKER, HAND KLIMA, R.: Zur Kenntnis der plasmazellularen Leukemie, *Folia haemat.*, 56: 5, 1936.
15. SCHILLING, V., AND WOHLBERG, W.: Über Plasmazellenleukemie, *München. med. Wchnschr.*, 85: 1292, 1938.
16. LACHNITT, V., AND WALTERSKIRCHEN, L.: Ein Fall von plasmazellularen Leukemie, *Wien. klin. Wchnschr.*, 52: 67, 1939.
17. ASKANAZY, M., AND DUBOIS-FERRIERE, H.: La cellule plasmatique et la leucemie plasmacellulaire, *Helvet. med. acta*, 9: 427, 1942.
18. RUBIN, G.: Report of two cases of multiple myeloma with plasma cells in the circulating blood, *Bull. Hosp. Joint Dis.*, 3: 62, 1942.

# THE DISSEMINATION AND CONTROL OF MENINGOCOCCAL INFECTIONS<sup>1</sup>

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The sudden onset and the striking clinical features, coupled with the variable and high case fatality rate, have served to sharply delineate cerebrospinal fever. The infrequent demonstration of association between cases of this apparently highly infectious disease and the ineffectiveness of quarantine or other control measures have increased, disproportionately, the fear of attack. The anxiety associated with any potentially epidemic infection is inversely proportional to the degree of knowledge as to the modes of transmission and the practicability and efficacy of protective procedures.

A wave of meningococcal infections has followed in the wake of the vast industrial and military mobilization in the British Isles (1), Canada (2) and the United States (3, 4). During the years 1942, 1943 and 1944 a marked increase in the incidence of meningococcal meningitis and meningococcemia has been noted in this country, amounting to approximately ten times the five year median, 1937-1941. It has been observed in both civilian and military populations (3, 4, 5, 6). This epidemic has been the greatest recorded by the United States Public Health Service during the past 40 years and far exceeds the preceding epidemics of 1917-18, 1929-30 and 1936-37 (5).

Cerebrospinal fever was recognized as a clinical and epidemiological entity early in the 19th century. Owing to the skin eruption frequently present, it was called "sinking typhus," "cerebral typhus" and "spotted fever" and confused with classical typhus fever. Because of the prominence of symptoms arising from the inflammatory process in the central nervous system, it has had such designations as "brain fever," "acute hydrocephalus," "encephalitis," "cerebrospinal fever" and "cerebrospinal meningitis" (7).

The term "epidemic" has always been associated with the occurrence of meningococcus meningitis, yet it has long been recognized that sporadic cases occur and, in any large population, periods of low or endemic prevalence alternated with periods when the disease became unusually prevalent or epidemic. The length of the interval between epidemic periods and the area affected has been uncertain but that they occurred was clear to all those who reviewed the literature.

<sup>1</sup> These investigations were aided by the Commission on Meningococcal Meningitis, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of The Surgeon General, War Department.

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The etiologic agent was first seen in preparations from the spinal fluid by Marchiafava and Celli (8) in 1884, but credit is given to Weichselbaum (9) for the cultivation and positive identification of the causative organism, *Diplococcus intracellularis meningitidis* or *Neisseria intracellularis*, in 1887. It was not until the turn of the century that the etiologic rôle of this microorganism became fully established and accepted as a result of investigations made in many parts of the world, notably by Councilman, Mallory and Wright (10), Elser and Huntoon (11), and Flexner and his associates (12) in the United States; by Albrecht and Ghon (13) in Germany; by Dopter (14), Netter and Debré (15) in France; by Gordon (16) in England, and others. Between 1900 and 1910 the practice of making lumbar puncture became a commonly accepted diagnostic procedure, and physicians began to separate cerebrospinal meningitis due to the meningococcus from meningitis due to other causes. Thereafter, "meningococcus meningitis," an etiologic designation, came into general use.

As bacteriological methods improved and observations were extended, it was discovered that the first site of infection with the meningococcus was in the rhinopharynx and in a considerable proportion of cases, the organism could be recovered from the blood stream. In fatal cases post mortem examination frequently revealed hematogenous metastatic foci in the heart, spleen, skin and other tissues. Meningococcemia sometimes occurred without extension of the infection to the meninges.

More important, in 1901, Albrecht and Ghon (13) called attention to the fact that not only cases but many apparently normal individuals who, in so far as was known, had not had any contact with clinical meningococcal infection, harbored meningococci in their rhinopharynx. The existence of "carriers" afforded an explanation for much that had been obscure as to the manner of spread of this disease. This observation was confirmed and many studies were conducted to determine the frequency and importance of these infections during epidemic and interepidemic periods (17, 18, 19). Since the World War I of 1914-18, it has been realized to an increasing degree that cerebrospinal meningitis is, in a sense, a complication occurring occasionally among those who become infected with the meningococcus.

Bacteriologists have sought to identify the particular strains which were capable of invading the tissues of the host and to understand the factors concerned in resistance to such sequelae. Dopter (20), in 1909, described nasopharyngeal strains which were indistinguishable from those isolated from the spinal fluid of cases except for differences in their agglutination reaction. Later it was shown that these "parameningococci" could be isolated from typical clinical cases of meningitis. Since then, many workers have arranged further groupings, employing in some instances only case strains and in others, case and "non-contact carrier" strains. Gordon and Murray in 1915, by systematic use of the agglutination absorption reaction with strains isolated from military cases, demonstrated that these meningococci could be divided into four distinct types which they called I, II, III and IV (21). This classification found general

acceptance in England and America. It was used by Branham (22) in her serological typing of case strains isolated between 1928 and 1930 in the United States. Rake (23), through his work with the specific polysaccharides, combined Types I and III into Group I. Branham and Carlin (24) have recently added a new serological type for which they suggest the designation Type II alpha. Serological typing of 2,270 strains isolated from cases in 1942 and 1943 among Army personnel, by the Commission on Meningococcal Meningitis, has shown that 91.0 per cent were Group I, 5.5 per cent Type II alpha, and 3.1 per cent Group II.

Glover (25) has suggested that a "non-contact carrier rate" of 20 per cent or more is a danger signal which presages the occurrence of cases of cerebrospinal fever. However, Dudley and Brennan (26), among others, have found high "carrier rates" in populations where clinical meningococcal infections were not occurring. Maxcy (27) and Dingle and Finland (28), in their reviews, have questioned the importance attached to crude carrier percentages. Also it has not been fully appreciated that the presence of large numbers of nasopharyngeal "carrier" infections during outbreaks of meningococcal meningitis while required, must be accompanied by other essential conditions. In other words, during periods of unusual prevalence, the "high carrier rates" comprise only a necessary but etiologically insufficient condition.

The term "carrier" has many connotations which interfere with a clear understanding of the host-parasite relationships. It can be interpreted to imply that the individual may act as a passive vector. It is difficult to concede, however, that living animal tissue can be the site of multiplication of any organism without reacting in some way to its presence. The relation to such multiplication may be so slight and transient as to escape recognition and be discernible only as an altered response of the host tissue such as antibody formation. It may be so severe as to be obvious to all observers. Reactions in all possible gradations must be considered "infections."

Individuals harboring the meningococcus in their nasopharynx are said by Netter and Debré (29) to exhibit a local inflammatory reaction to its presence. This observation has not been satisfactorily confirmed. The consensus of opinion at present does not accept any distinct specific inflammatory reaction. Whether an antibody response occurs among this group is unknown because the diagnostic methods available are too crude and complicated. Specific bactericidal activity has been obtained with sera of apparently normal individuals who, to their knowledge, have not had a previous meningococcal infection.

Rake (30), in his study of an epidemic, states: "Despite the absence of any convincing local infection in meningococcus carriers, this general reaction of the body would seem to point to the fact that the carrier state is to be looked upon as an infection." There is no reason to believe that the spectrum of infection with the meningococcus differs qualitatively from that of *C. diphtheriae*, *H. influenza*, *Streptococcus hemolyticus* Beta and others. In all these diseases, a certain proportion of the population becomes immunized as a result of minor, atypical, inapparent, or unrecognizable infections.

The classification of "carriers" as infected individuals implies that the clinical syndromes such as nasopharyngitis, meningococcemia, or meningitis are expressions of the degree of invasion rather than any fundamental difference in host-parasite relationships. With this concept, cases can be considered uncertain and irregular indicators of the spread of meningococcal infections in a population. The real flow is submerged and can be revealed solely by uncovering subclinical or inapparent infections.

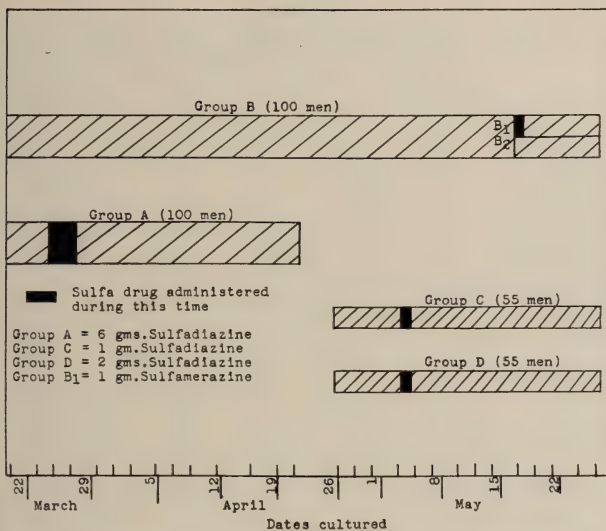


FIG. 1. Relationship of groups to time of culture and administration of drug

The Commission on Meningococcal Meningitis arranged an investigation during the spring of 1943 at a large Army camp, (1) to describe the dynamics of subclinical meningococcal infections, according to type, in respect to distribution, prevalence, incidence and duration; and (2) to determine the minimal effective dose of sulfonamides required to obtain parasitic cure of these infections. The size of the samples, the interval between cultures, and the techniques employed, were so planned as to furnish valid answers. The orientation in time of the study and the relationships of the various groups is presented in Figure 1.

In summary, it may be stated that Group "A" received six grams of sulfadiazine and its effect was noted for one month. Group "C" received one gram and Group "D" two grams of sulfadiazine and were followed for approximately three weeks. Group "B" served as the control for groups "A", "C" and "D",

and for the study of the dynamics of subclinical infections. The last week, one-half of Group "B" was given one gram of sulfamerazine.

The results of this investigation disclose several important aspects of the dynamics of inapparent meningococcal infections among Army personnel. The average composite prevalence rate among the control group "B" was 40 per cent. These results are summarized in Table 1. The number of subclinical meningococcal infections found during the ten week study period is presented in Table 2.

TABLE 1  
*Frequency of type specific meningococci in nasopharyngeal cultures*

| RESULT OF CULTURE              | NUMBER | PER CENT OF TOTAL CULTURES |
|--------------------------------|--------|----------------------------|
| <i>Single Type</i> .....       | 949    | 38.8                       |
| Group I.....                   | 350    | 14.3                       |
| Type IIa.....                  | 220    | 9.0                        |
| Group II.....                  | 370    | 15.1                       |
| Group II-IIa.....              | 9      | 0.4                        |
| <i>Two or More Types</i> ..... | 31     | 1.3                        |
| Group I and IIa.....           | 2      | 0.08                       |
| Group I and II.....            | 12     | 0.5                        |
| Group I and II-IIa.....        | 1      | 0.04                       |
| Group II and IIa.....          | 12     | 0.5                        |
| Group II and II-IIa.....       | 3      | 0.1                        |
| <i>Total Containing</i>        |        |                            |
| Group I.....                   | 365    | 14.8                       |
| Type IIa.....                  | 235    | 9.5                        |
| Group II.....                  | 398    | 16.1                       |
| Group II-IIa.....              | 13     | 0.5                        |
| Total Positive.....            | 980    | 40.0                       |
| Total Negative.....            | 1,471  | 60.0                       |
| Total.....                     | 2,451  | 100.0                      |

Of the 99 men in the control group, 92.9 per cent were infected at some time during the study period. Of the 92 positive men, 44 had infections classified as "persistent" under a reasonable definition. An approximately equal number had only "transient" infections. Classification of the plates according to the type and number of meningococcal colonies present did not differentiate between the "persistent" and "transient" infections.

No fixed pattern could be derived from the study of the individual records. Some men were negative throughout the study period. In many, infection was followed by spontaneous parasitic cure. In others, infections with one type would be followed, interrupted, or accompanied by an infection with another type.

No correlation could be demonstrated between the daily prevalence rates, climatic conditions, the occurrence of upper respiratory disease, or the incidence of the common contagious diseases, including clinical meningococcal infections.

The frequency distribution of meningococcal types as isolated from cases was not duplicated when subclinical infections were studied. All the clinical cases at this camp had been associated with the Group I meningococcus. Typing of the strains isolated from cases throughout the Army had shown that 91.0

TABLE 2

*Number of men with subclinical meningococcal infections during the 10 week study period*

| RESULT OF CULTURES               | NUMBER OF MEN | PER CENT OF TOTAL |
|----------------------------------|---------------|-------------------|
| <i>Single Type</i> .....         | 48            | 48.5              |
| Group I.....                     | 22            | 22.2              |
| Type IIa.....                    | 11            | 11.1              |
| Group II.....                    | 15            | 15.2              |
| Group II-IIa.....                | 0             | 0.0               |
| <i>Two or More Types</i> .....   | 44            | 44.4              |
| Group I and IIa.....             | 8             | 8.1               |
| Group I and II.....              | 14            | 14.1              |
| Group I and II-IIa.....          | 1             | 1.0               |
| Type IIa and II.....             | 10            | 10.1              |
| Type IIa and II-IIa.....         | 0             | 0.0               |
| Group II and II-IIa.....         | 2             | 2.0               |
| Group I, IIa and I.....          | 6             | 6.1               |
| Type IIa, II and II-IIa.....     | 1             | 1.0               |
| Group I, IIa, II and II-IIa..... | 2             | 2.0               |
| <i>Total Harboring</i> .....     |               |                   |
| Group I.....                     | 53            | 53.5              |
| Type IIa.....                    | 38            | 38.4              |
| Group II.....                    | 40            | 40.4              |
| Group II-IIa.....                | 6             | 6.1               |
| Total Positive.....              | 92            | 92.9              |
| Total Negative.....              | 7             | 7.1               |
| Total.....                       | 99            | 100.0             |

per cent were Group I. Among the 99 men in control group "B", 53.5 per cent of the subclinical infections were Group I, 38.4 per cent were Type II alpha and 40.4 per cent were Group II.

The high proportion, 92.9 per cent, of the 99 men found infected, extended and confirmed the concept that the spread of the meningococcus was primarily at the subclinical level. Only seven escaped infection during the brief period of 68 days, indicating the extent and rapidity of flow.

It is apparent that the composite or type specific prevalence rate for any given day or for the study period as a whole is a static representation of a biologic



equilibrium and does not describe the rate of transmission of the meningococcus. A dynamic process exists and must be illustrated by a dynamic equation. The number of new infections in each succeeding time period, that is, the incidence rate, is a much better index than the level of prevalence attained. If the incidence is increasing, transmission is taking place; if it is decreasing, conditions are operating against the survival of the parasite. The same prevalence may be found in two population groups, yet in one there may be a declining and in the other an increasing transmission of the meningococcus. If all other factors were equal such as group susceptibility or degree of contact, the latter situation would cause more concern.

With this concept, the hypothesis of a "fixed epidemic level" of subclinical meningococcal infection fails. Glover (25) concluded that there was a correlation between prevalence of subclinical infections and the incidence of clinical cases by stating: "A carrier rate of 20 per cent (without awaiting the occurrence of cases) should be regarded as a signal for prompt and effective action." However, in the development of this thesis, he was actually concerned with the changes in prevalence rather than the static level. In his report, the following inferences were drawn: "A wave of high (non-contact) carrier rates preceded and accompanied an outbreak of cerebrospinal fever... there is a carrier epidemic (for the most part entirely devoid of symptoms) preceding and accompanying the much smaller case epidemic." He did not stress sufficiently the importance of this latter observation and later workers have neglected it entirely. From this and other studies of the Commission on Meningococcal Meningitis during the past two years, it has been evident that the number of cases would be determined by the incidence of new infections, rather than their prevalence, in any given period.

These observations also offer an explanation for the failure of control measures which have been suggested in the past. The meningococcus must be considered an "efficient parasite" which maintains itself in any human population through infections at a subclinical level. Only a very small proportion of the total number of infections are followed by clinical manifestations. The latter group acquire the parasite not necessarily from contact with other cases but from apparently healthy individuals who have a subclinical or inapparent infection. As there are no methods for the protection of susceptibles, a reduction in the number of clinical cases can be obtained only by decreasing the probability of exposure to the meningococcus.

Four measures have been commonly employed to interrupt transmission of a pathogen, (1) isolation of the identified infected individual; (2) the treatment of the infected individual; (3) sterilization of the medium of transmission; and (4) protection of the recipient by immunization. The first two have failed with the meningococcus because, despite the threshold employed, there is no feasible method of identifying all these suspected foci. The possibility of reducing transmission by sterilizing the air of enclosed living spaces with aerosols or ultraviolet radiation is still being explored but to the present, has not been demonstrated to be of practical value. The lack of any successful immunizing

antigen precludes the use of the fourth method. For control, the entire population must be considered as the unit, and attention directed toward those factors which determine the constants of the biologic equilibrium. It is almost impossible, under the conditions of human intercourse existing today, to change these factors to any appreciable extent. The risk of exposure to the meningococcus can be reduced only if parasitic cure of the infected individuals in a population is obtained *without resort to their specific identification*.

The sulfonamides have been suggested for the eradication of the meningococcus from the nasopharynx (31, 32). There are certain administrative difficulties and hazards encountered whenever extensive drug therapy is instituted. It is accepted that some individuals are or will be sensitized to the sulfonamides. The latter usually follows continued administration or repeated courses. The meningococcus, furthermore, in view of the experience with the gonococcus, may become drug-fast. One of the phases of this study was to determine the optimal dose suitable for mass administration.

The drugs were administered orally under direct supervision. Group "A" received one gram of sulfadiazine twice daily for three days, a total dosage of six grams. One and two grams of the same drug were given as a single dose to the men in Groups "C" and "D", respectively. Group "B<sub>1</sub>" received a single gram of sulfamerazine.

No toxic reactions, such as rash, fever, urinary complaints, nausea or malaise, were encountered. A few noted dryness of the throat and two who had received six grams complained of a mild headache during the course of therapy. No subjective visual disturbances were elicited. Hematological studies and urinalysis revealed no abnormality attributable to the drugs. None of the men had a history of prior ingestion of these sulfonamides.

The criteria selected to assess the efficiency of the chemotherapeutic procedures were:

- (1) comparative and absolute reduction of the prevalence level;
- (2) the length of the resultant negative interval;
- (3) the frequency of persistence or recurrence of infections with the same type of meningococcus.

The first of these is most easily measured and most apparent. However, the change in the prevalence level does not differentiate between suppression below the threshold of identification and eradication of the meningococcus from the nasopharynx. For this characterization, the last two indices must be employed. For their determination, the same groups must be cultured regularly for a definite period of time. They are influenced by other factors such as the incidence of meningococcal infections in the untreated group and the degree of re-exposure of the treated men. Therefore, these two criteria cannot be used for the evaluation of different studies, even though the technical methods are similar.

The prevalence of subclinical meningococcal infections among the groups receiving the sulfonamide drugs as compared with a concomitantly cultured control group is graphically presented in Figures 2a, 2b, 2c, and 2d.

In these trials parasitic cure was obtained with two or more grams of sulfadiazine. The one gram doses of sulfadiazine or sulfamerazine were followed by

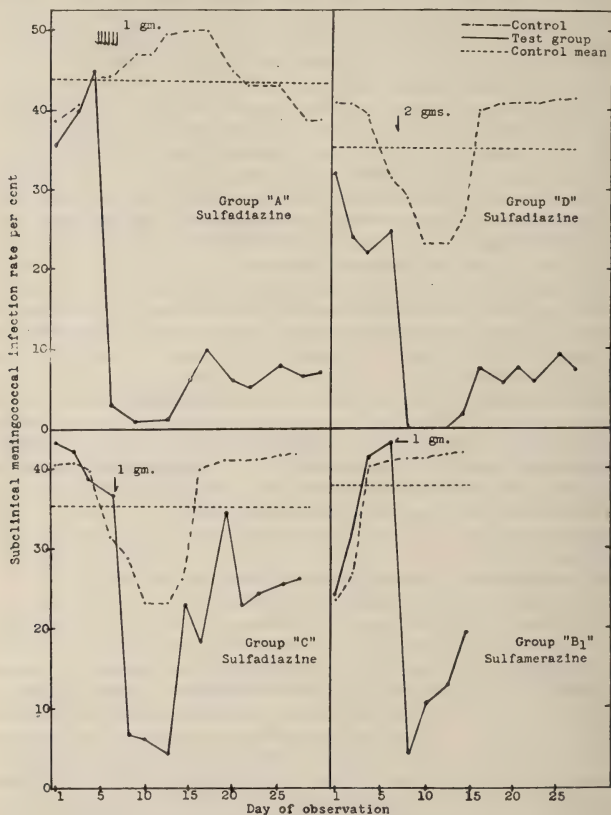


FIG. 2. Subclinical meningococcal infections in drug treated groups

parasitic cure in some and only suppression in others. This conclusion was based upon the observations summarized below and in Table 3.

(1) Immediately subsequent to the administration of two or more grams of drug to the 154 men in Groups "A" and "D", all the 85 known prior infections

became negative. Only one positive result was obtained in an individual who had been negative on four previous occasions. When one gram was given to the 103 men in Groups "C" and "B<sub>1</sub>", 5 of the 61 prior infections persisted through the first post-drug culture.

(2) The reduction in the average prevalence level of Groups "A" and "D" when compared with the results of the concomitantly cultured control group "B" exceeded 85 per cent for the post-drug period. This reduction in Groups "C" and "B<sub>1</sub>" averaged about 60 per cent.

TABLE 3  
*Subclinical meningococcal infections in the post-sulfonamide period*

| GROUP          | DRUG          | DOSAGE | NUMBER OF MEN IN GROUP | POST-SULFONAMIDE PERIOD |       |                | AVERAGE PREVALENCE OF SUBCLINICAL MENINGOCOCCAL INFECTION |      |           | AVERAGE INTERVAL IN DAYS FROM FINAL DAY OF DRUG TO FIRST POSITIVE CULTURE |           |               | SUBCLINICAL MENINGOCOCCAL INFECTIONS |                                  |                         |                         |            |                         |
|----------------|---------------|--------|------------------------|-------------------------|-------|----------------|---|------|-----------|---|-----------|---------------|--------------------------------------|----------------------------------|-------------------------|-------------------------|------------|-------------------------|
|                |               |        |                        | Observation             |       |                | Prior to drug   | Post | Reduction | All types   | Same type | Changed type* | Total prior to drug                  | Following administration of drug |                         |                         |            |                         |
|                |               |        |                        | Begun                   | Ended | Number of days |   |      |           |   |           |               |                                      | Any type                         | Recurrence of same type |                         |            |                         |
|                |               |        |                        |                         |       |                |   |      |           |   |           |               |                                      |                                  | 0-9 days                |                         | 10-19 days |                         |
|                |               |        |                        |                         |       |                |   |      |           |   |           |               |                                      |                                  | Number                  | Per cent of total prior | Number     | Per cent of total prior |
| A              | Sulfa-diazine | 6 gms. | 99                     | 3/26                    | 4/21  | 26             | 40.0  | 5.1  | 87.5      | 14  | 14        | 15            | 58                                   | 26                               | 1                       | 1.7                     | 3          | 5.2                     |
| D              | Sulfa-diazine | 2      | 55                     | 5/4                     | 5/26  | 22             | 25.7  | 4.6  | 82.2      | 14  | 16        | 16            | 27                                   | 11                               | 1                       | 3.7                     | 3          | 11.1                    |
| C              | Sulfa-diazine | 1      | 55                     | 5/4                     | 5/26  | 22             | 40.8  | 19.1 | 51.8      | 8   | 9         | 7             | 37                                   | 26                               | 8                       | 21.6                    | 8          | 21.6                    |
| B <sub>1</sub> | Sulfamerazine | 1      | 48                     | 5/17                    | 5/26  | 9              | 35.4  | 11.8 | 66.7      | 6   | 6         | 6             | 24                                   | 12                               | 9                       | 38.2                    |            |                         |

\* Negative to positive or different type are included under this heading.

(3) Comparison of the average prevalence level before and after drug in Groups "A" and "D" revealed a reduction of over 80 per cent, while that for the other groups was approximately 60 per cent.

(4) The length of the resultant negative interval when all types of meningococci were considered was 14 days for Groups "A" and "D" and 6-8 days for Groups "C" and "B<sub>1</sub>." Calculation of this interval with respect to the recurrence of the same type or the occurrence of new infections as manifested by change of type, revealed no material differences.

(5) The maximum incidence of recurrent infections with the same type of meningococcus in Groups "A" and "D" was 6.9 per cent and 14.8 per cent, respectively. In contrast, the incidence of recurrence was 43.2 per cent for Group "C" and 38.2 per cent for Group "B<sub>1</sub>."

The use of the sulfonamides, therefore, offers a feasible method of rapidly decreasing the prevalence of meningococcal infections in any limited group. Increasing the amount of drug given as a single dose, or repeating the dosage, would merely extend the period of meningococcal activity, provided an adequate drug level be attained or maintained.

Prophylaxis by chemotherapy, however, cannot control the incidence of re-infections indefinitely. It must be recognized that only immediate parasitic cure or suppression is obtained. There may be a brief refractory period following the administration of the drug, due possibly to a change in the nasopharyngeal bacterial flora. However, there are no grounds, either theoretical or experimental, for the assumption that the sulfonamides, except during the relatively brief period of their activity, confer freedom from, or enhance resistance to, subsequent infection over any long period of time. The rapidity with which the treated groups will attain the prevalence level of the general community will depend upon their degree of re-exposure. Exposure is a resultant of the *effective contact rate* between the treated and untreated groups and the *incidence*, as contrasted to the prevalence, of meningococcal infection, among the latter. Any plan for prophylaxis by chemotherapy must consider these factors, and not be determined arbitrarily.

#### SUMMARY

The dynamics of subclinical meningococcal infections according to type in respect to distribution, prevalence, incidence and duration were studied in a control group chosen at random from an Army medical service unit. The men were cultured regularly three times a week for ten weeks. With an average composite prevalence rate of 40 per cent, infections with at least one of the several types of the meningococcus were found in 92.9 per cent of the men during the study period. Although the Group I meningococcus was the prominent clinico-pathogenic strain, it was revealed that the other types were equally prevalent when subclinical infections were studied. The composite or type specific prevalence rates for any day or for the study period as a whole represented the biologic equilibrium between host and parasite. The level maintained was a resultant of the incidence and recovery rates of subclinical infections among this group.

The administration of two or more grams of sulfadiazine to men chosen from the same unit was followed by parasitic cure unaccompanied by any toxic reactions. Two grams was thus chosen as the optimal dose for mass prophylaxis. Later this was found to be insufficient for prolonged effect.

The meningococcus is simply one of the many potentially pathogenic microorganisms that make their way from the nasopharynx of one individual to that of another. In this transfer from one host to another, the vast majority of individuals develop sufficient immunity to resist invasion of the blood stream and localization in the meninges. The clinical case is a relatively infrequent but dramatic manifestation which reflects the flow of this parasite through the population. Where indicated, group chemotherapy offers a feasible means of



controlling the meningococcal prevalence rate without requiring identification of the individuals infected at the subclinical level.

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#### BIBLIOGRAPHY

- (1) Weekly and Quarterly Returns of the Registrar General, London, H. M. Stationery Office, 1941, 1942 and 1943.
- (2) DINGLE, J. H., THOMAS, L. AND MORTON, A.: Treatment of meningococcic meningitis and meningococemia with sulfadiazine. *J. A. M. A.*, 116: 2666, 1941.
- (3) Morbidity and Mortality from Specific Causes During 1942 and Recent Preceding Years. *Weekly Public Health Rep.*, 58: 730, 1943.
- (4) Meningococcus Meningitis in the United States during 1943. *Weekly Public Health Rep.*, 59: 469, 1944.
- (5) Prevalence of Disease (United States). *Weekly Public Health Rep.*, 59: 883, 1944.
- (6) Records and Cultures of cases received by and on file with the Commission on Meningococcal Meningitis, U. S. Army.
- (7) HIRSCH, A.: Epidemic cerebrospinal meningitis. *Handbook of Geographical and Historical Pathology* (Translated by Charles Creighton), London, The New Sydenham Society, 3: 547, 1886.
- (8) MARCHIAFAVA AND CELLI: Cited in HIRSCH (7), 587.
- (9) WEISCHSELBAUM, A.: Ueber die aetiologie der akuten meningitis cerebrospinalis. *Fortschr. d. Med.*, 5: 573, 1887.
- (10) COUNCILMAN, W. F., MALLORY, F. B. AND WRIGHT, J. H.: Epidemic cerebrospinal meningitis and its relation to other forms of meningitis. Report of the State Board of Health of Massachusetts, 1898.
- (11) ELSE, W. J. AND HUNTOON, F. M.: Studies on meningitis. *J. Med. Research*, 20: 377, 1909.
- (12) FLEXNER, S. AND BARKER, L. F.: A contribution to our knowledge of epidemic meningitis. *Am. J. M. Sc.*, 107: 155, 1894.
- (13) VON ALBRECHT AND GHON, A.: Ueber die aetiologie und pathologische anatomie der meningitis cerebrospinalis epidemica. *Wien. klin. Wchnschr.*, 14: 984, 1901.
- (14) Dopter, C.: L'infection meningococcique. Paris, J. B. Bailliere et fils, 1921.
- (15) NETTER, A. AND DEBRÉ, R.: La meningite cerebrospinale. Paris, Masson et Cie, 1911.
- (16) GORDON, M. H.: Bacteriological studies in the pathology and preventive control of cerebrospinal fever among the forces during 1915 and 1916. *Med. Res. Council, Spec. Rep. Series No. 3*, 1916.
- (17) Cerebrospinal fever. Studies in the bacteriology, preventive control and specific treatment of cerebrospinal fever among the military forces, 1915-1919. *Med. Res. Council of the Privy Council, Spec. Rep. Series No. 50*, London, H. M. Stationery Office, 1920.

- (18) ROSSITER, P. S. AND MINAKER, A. S.: The examination of 8,518 men for the detection, isolation and treatment of meningococcus carriers at the United States Naval Training Station, San Francisco, California. *U. S. Naval Med. Bull.*, 12: 195, 1918.
- (19) RAKE, G.: Studies on meningococcus infection. VI. The carrier problem. *J. Exper. Med.*, 59: 553, 1934.
- (20) DORTER, C.: Etude de quelques germes isolés du rhino-pharynx, voisins du meningocoque (parameningocoque). *Compt. rend. Soc. de Biol.*, 67: 74, 1909.
- (21) GORDON, M. H. AND MURRAY, E. G.: Identification of the meningococcus. *J. Roy. Army M. Corps*, 24: 411, 1915.
- (22) BRANHAM, S. E., TAFT, C. E. AND CARLIN, S. A.: Studies on meningococci isolated in the United States, 1928-1930: Serological classification and geographical distribution. *Weekly Public Health Rep.*, 46: 897, 1931.
- (23) RAKE, G. AND SCHERP, M. W.: Studies on meningococcus infection. III. The antigenic complex of the meningococcus: A type specific substance. *J. Exper. Med.*, 58: 341, 1933.
- (24) BRANHAM, S. E. AND CARLIN, S. A.: Comments on a newly recognized group of the meningococcus. *Proc. Soc. Exper. Biol. & Med.*, 49: 141, 1942.
- (25) GLOVER, J. A.: Cerebrospinal fever: Studies in the bacteriology, preventive control and specific treatment of cerebrospinal fever among the military forces, 1915-1919. Section 20. Observations of the meningococcus carrier rate and their application to the prevention of cerebrospinal fever. *Med. Res. Council of the Privy Council, Special Rep. Series No. 50*, London, H. M. Stationery Office, page 133, 1920.
- (26) DUDLEY, S. F. AND BRENNAN, J. R.: High and persistent carrier rates of *Neisseria meningitidis* unaccompanied by cases of meningitis. *J. Hyg.*, 34: 525, 1934.
- (27) MAXCY, K. F.: The relationship of meningococcus carriers to the incidence of cerebrospinal fever. *Am. J. M. Sc.*, 193: 438, 1937.
- (28) DINGLE, J. H. AND FINLAND, M.: Diagnosis, treatment and prevention of meningococcic meningitis. *War Medicine*, 2: 1, 1942.
- (29) NETTER, A. AND DEBRÉ, R.: La meningite cerebrospinale. Chapter III. Paris, Masson et Cie, page 37, 1911.
- (30) RAKE, G.: Studies on meningococcus infection. VIII. The study of an isolated epidemic. *J. Exper. Med.*, 61: 545, 1935.
- (31) MEEHAN, J. F. AND MERRILLEES, C. R.: An outbreak of cerebrospinal meningitis in a founding hospital. The treatment of carriers with "M & B 693." *M. J. Australia*, 2: 84, 1940.
- (32) FAIRBROTHER, R. W.: Cerebrospinal meningitis. The use of sulfonamide derivatives in prophylaxis. *Brit. M. J.*, 2: 859, 1940.

## STAPHYLOCOCCIC PULMONARY ABSCESS DUE TO TRAUMA OF THE SKIN

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Prior to the advent of penicillin, pulmonary abscess due to staphylococcemia was not well recognized. This was especially due to the fact that most of the patients failed to live long enough for this complication to become clinically apparent.

At necropsy it was usually found that many miliary abscesses in the lungs were present in conjunction with thrombophlebitis of the pulmonary veins in the region of the abscesses. The mortality in the past, according to various observers ranged from 66 per cent (Rosenow and Brown) (1) and upward to 75 per cent (MacNeal and Frisbee) (2), 81.97 per cent (Skinner and Keefer) (3), 83 per cent (Theodore Mendell) (4), and 91.7 per cent (Ottenberg) (5).

The use of penicillin has substantially reduced the number of deaths from staphylococcemia. According to Wallace E. Herrel (6), 4 of his 28 patients died. Dawson and Hobby (7), report 18 cases, of which 3 were fatal; other reports are similar. However, the incidence of pulmonary complications remains fairly high. In one institution with which the author is associated,<sup>1</sup> three patients with pulmonary abscess following staphylococcemia treated with penicillin have recovered within the last two months. In each case, however, the pulmonary abscess required surgical treatment.

The importance of the relationship of trauma of the skin to these conditions is not sufficiently recognized since the injury may be very trivial or apparently healed when the pulmonary abscess and staphylococcemia develop. Furthermore, there seems to be no time limit to the interval between the occurrence of the trauma and the appearance of the bacteremia. It may be 24 hours, or several weeks (8).

The following case afforded an excellent opportunity for the study of these problems.

### CASE REPORT

*History:* B. G., aged 50 years, born in Poland, a tailor, married, was admitted to the Medical Service of the Beth-El Hospital on September 18, 1943.

*Past history:* About five years prior to his admission the patient had had a tonsillectomy, at which time a routine examination revealed glycosuria. The blood sugar was normal at that time and remained so until the day he entered the hospital when glycosuria was again discovered. He had been on a regular diet and had apparently never been seriously ill. There was no history of venereal disease or other infections.

On September 3, 1943 the patient was seized with a chill followed by a rise in temperature to 104 degrees F. He complained of a severe pain in the chest and a hacking cough. A

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<sup>1</sup> Beth-El Hospital, Brooklyn, N. Y.

diagnosis of bronchopneumonia was made by the attending physician. The patient's temperature fluctuated between 101 and 104 degrees F. for three days, and then remained normal for about four days. This was followed by chills and fever for two days followed by another three day period of remission, after which the chills and fever recurred for the third time. He was placed on sulfadiazine therapy. In view of the patient's serious condition and the uncertainty of the diagnosis he was hospitalized.

*Examination:* The patient was a well developed individual and appeared to be very toxic. The right chest revealed dullness, diminished breath sounds, and a few scattered râles together with some limitation of motion. The heart was not enlarged. The apex was in the mid-clavicular line, the sounds were of good muscular quality, and the rhythm was regular. There was no murmur audible. The blood pressure showed a systolic of 110 and a diastolic

TABLE 1

| DATE     | HEMO-<br>GLOBIN | RED BLOOD<br>COUNT | WHITE<br>BLOOD<br>COUNT | SEGMENT-<br>TERS | STABS | TOTAL<br>LYMPHO-<br>CYTES | TOTAL<br>MONO-<br>CYTES | PLATELETS | EOSINO-<br>PHILES |
|----------|-----------------|--------------------|-------------------------|------------------|-------|---------------------------|-------------------------|-----------|-------------------|
|          | %               |                    |                         |                  |       |                           |                         |           |                   |
| 9/19/43  | 80              | 4,850,000          | 10,500                  |                  |       |                           |                         |           |                   |
| 9/24/43  | 78              | 3,890,000          | 6,000                   | 50               | 30    | 16                        | 3                       | 240,000   | 1                 |
| 10/ 5/43 | 52              | 3,100,000          | 5,000                   | 59               | 19    | 19                        | 2                       | 250,000   | 1                 |
| 10/ 6/43 | 52              | 3,100,000          | 8,300                   |                  |       |                           |                         |           |                   |
| 10/ 7/43 | 53              | 3,320,000          | 8,000                   |                  |       |                           |                         |           |                   |
| 10/ 8/43 | 52              | 3,120,000          | 7,700                   |                  |       |                           |                         |           |                   |
| 10/11/43 | 47              | 2,540,000          | 5,700                   |                  |       |                           |                         |           |                   |
| 10/12/43 | 48              | 2,750,000          | 5,700                   |                  |       |                           |                         |           |                   |
| 10/13/43 | 49              | 2,950,000          | 3,400                   |                  |       |                           |                         |           |                   |
| 10/14/43 | 49              | 2,900,000          | 2,500                   |                  |       |                           |                         |           |                   |
| 10/15/43 | 46              | 2,680,000          | 2,700                   |                  |       |                           |                         |           |                   |
| 10/16/43 | 47              | 2,850,000          | 4,000                   |                  |       |                           |                         |           |                   |
| 10/18/43 | 47              | 2,720,000          | 3,900                   |                  |       |                           |                         |           |                   |
| 10/19/43 | 48              | 3,500,000          | 3,000                   | 56               | 16    | 26                        | 2                       |           |                   |
| 10/20/43 | 48              | 3,100,000          | 3,800                   | 55               | 14    | 28                        | 3                       |           |                   |
| 10/22/43 | 52              | 3,200,000          | 3,800                   | 59               | 15    | 23                        | 3                       |           |                   |
| 10/23/43 | 52              | 3,260,000          | 2,600                   | 52               | 15    | 30                        | 3                       |           |                   |
| 10/26/43 | 58              | 3,310,000          | 2,800                   | 60               | 8     | 32                        |                         |           |                   |
| 10/28/43 | 62              | 3,400,000          | 3,000                   | 60               | 6     | 30                        | 4                       |           |                   |
| 11/ 2/43 | 65              | 3,650,000          | 4,000                   | 64               | 3     | 30                        | 3                       |           |                   |
| 11/ 3/43 |                 |                    | 4,000                   |                  |       |                           |                         |           |                   |
| 11/ 4/43 | 71              | 3,750,000          | 4,600                   | 56               |       | 38                        | 6                       |           |                   |

of 70. The temperature was 104 degrees F. The pulse rate was 106 and respirations numbered 24. A diagnosis of bronchopneumonia was made which was confirmed by x-ray examination.

*Laboratory data:* The urine examination on admission showed a 4 plus albumin and 1.8 per cent sugar. These findings continued to be present until the tenth day when the urine became sugar free and remained so, but during the entire stay in the hospital due to alkalies administered with the sulfadiazine the urine was alkaline. Albumin 3 to 4 plus and 5 to 10 to 20 to 40 pus cells to the field with occasional clumping were found on microscopic examination during the entire stay in the hospital. There were about 1 to 3 red blood cells per field, hyaline and granular casts; the specific gravity ranged from 1.010 to 1.020.

*Blood counts:* Numerous blood counts were made and are shown in the following table:

*Sternal puncture:* On October 19, the following changes in the bone marrow were reported by Dr. M. Morrison:

Granulo-erythrocyte ratio 65:35, normal 85:15.

|                     |             |
|---------------------|-------------|
| myeloblasts.....    | 5           |
| metamyelocytes..... | 15          |
| myelocytes.....     | 40          |
| staphs.....         | 30          |
| polys.....          | 20          |
| megacaryocytes..... | 2 or 3 plus |

*Blood chemistry:* Many blood chemistry determinations were done, a few of which are listed hereby.

|                  | 9/20/43 | 9/27/43 | 11/5/43 |
|------------------|---------|---------|---------|
| Sugar.....       | 249     | 307     | 121     |
| Urea.....        | 13.5    | 10.9    | 11.5    |
| Phosphorous..... | —       | —       | 3.8     |
| Total Protein..  | —       | —       | 6.9     |

*Other laboratory data:*

|             |   |   |
|-------------|---|---|
| 9/20/43.... | Kline Test  | Negative  |
| 9/22/43.... | Blood Culture   | No growth after 2 days                                  |
| 9/23/43.... | Blood Agglutination Tests for Paratyphoid A and B, Brucella abortus, B. Proteus Ox 19 | Showed no agglutination in dilutions from 1/20 to 1/320 |
| 9/27/43.... | Typhoid O, H, Paratyphoid A, B, Proteus Ox 19, B. Abortus                             | Showed no agglutination in dilutions from 1/20 to 1/320 |
| 9/27/44.... | Culture of feces for <i>Ebertella typhosa</i> , Shigella and Salmonella organisms     | Negative  |

*Sputum examination:* Repeated examinations were negative for acid-fast bacillus on smear and concentration test.

Direct smear demonstrated mixed organisms, while the culture of sputum revealed *Staphylococcus aureus* predominating.

*Röntgen examination of the chest:* On September 20, 1943 (two days after admission) there was a diffuse proliferative infiltration of both pulmonic fields interpreted as bronchopneumonia. On re-study, three days later, the infiltration seemed to have increased. On October 4, x-ray showed a small amount of fluid at the left base which persisted for about two weeks. On October 29, there was no evidence of the pleural effusion but the previously noted infiltration was again observed.

*Course:* From the date of admission until about a week before discharge, a period of six weeks, the patient's condition was considered critical. The severity of infection and toxicity of the disease may be visualized from the serial blood counts shown in the above table and also from the sternal punctures. The persistent and progressive fall in the total leukocyte count with an extreme shift to the left, total absence of eosinophiles, marked lymphopenia, the presence of toxic granules with severe secondary anemia, indicated the seriousness of the disease, and to a certain extent, gave a clue to the prognosis.

The symptomatology and clinical picture coincided with the blood findings described above. The patient was drowsy, restless, and moaning most of the time. The lips were cyanotic, the face pinched and sallow. He was constantly bathed in perspiration, although he had a high temperature. He had chills almost daily, each one lasting from 10 to 15 minutes. The pulse was weak and thready, respiration shallow and labored, and there was present a persistent cough with mucopurulent expectorations.

The physical findings in the chest throughout the disease were few. There was a slight dullness and a few fine râles at the end of inspiration over both bases. On October 4 there



developed evidence of fluid in the left chest. This persisted for about two weeks, at which time the fluid appeared to have been absorbed. The heart sounds were poor and scarcely audible, no murmurs were present. The blood pressure was never above 110 systolic and 60 diastolic.

On September 28, the blood culture was reported positive for hemolytic *Staphylococcus aureus*. As a result of this finding, the patient's history was retaken and the following information was obtained:

About seven weeks before the onset of the present illness he had suffered an abrasion to his right forearm. At the site of this trauma to the skin he developed an abscess which suppurated and discharged a purulent exudate for about two weeks. This was finally healed. The onset of the present illness really started about two or three weeks after the infection had apparently healed completely. Observation at time of admission to the hospital revealed a small non-adherent scar on the ulnar aspect of the right forearm and a few tender glands in the right axilla. No lymphnodes were present in the left axilla.

On October 12, six days after the administration of penicillin, the blood culture became negative and continued so until October 25 when another positive *Staphylococcus* culture was reported. The sputum at this time showed mixed infection with *Staphylococcus aureus* predominating.

The temperature throughout this stay in the hospital was interesting and significant. It ranged from 100 degrees F. to 105 degrees F. from the day of admission to October 29, and was not influenced by the various sulfa drugs or penicillin as shown in Temperature Chart.

A severe diarrhea developed on October 10, three weeks after admission, which lasted several days, and was probably due to the severe toxemia of the disease. He also complained of pain in the right ankle which later became swollen and tender. Repeated x-rays of the ankle were negative.

While penicillin was being given through the intravenous route, the patient remained in a rather fixed position on his right side and as a result developed a marked edema of the right leg and entire right side of the body. With restriction of fluids and postural change, it disappeared rapidly, except for some residue in the ankle and leg, which later proved to be due to thrombophlebitis of the internal saphenous vein. Recovery was slow but complete except for some persistence of pain in the right ankle, and palpable glands in the right groin were present.

*Treatment:* Sulfathiazole therapy was instituted on admission, (1 gram every 4 hours) and was continued for 5 to 6 days, at which time the sulfa level in the blood was 10 mg. Chills and temperature persisted and it was deemed advisable to discontinue the sulfa drugs to see if the fever would continue. Sulfadiazine was given again until October 6, when penicillin therapy was instituted. The latter was given in doses of 100,000 units daily, intravenously for 3 days, and later 20,000 units every 4 hours intramuscularly until October 13, when our allotment of penicillin was exhausted. The blood culture became negative on October 12, and remained so, with the exception of that of October 25. The temperature was not influenced as shown in the following chart. On October 22 more penicillin was obtained and again administered in amounts of 10,000 units every four hours intramuscularly until October 28. The temperature became normal by October 29. Oxygen therapy had been instituted early in the disease. Eight blood transfusions were given in a period of 20 days, because of severe anemia and prostration. Patient also received liver extract, iron and various vitamins. Cortical adrenal extracts were given on several occasions when the patient was in complete shock. The diabetic status was well controlled with a diet of 150 grams of carbohydrate, 75 grams of protein, 50 grams of fat, and 15 units of insulin three times a day before meals.

Improvement started on October 28, although the patient showed evidence of marked loss of weight and general weakness. The physical findings in the chest and the enlarged glands in the right groin remained unchanged. He was discharged on November 11, 1943.

*Re-admission:* The patient remained fairly well for a few weeks after discharge when the glands in the right groin became swollen and a large abscess formed. This had to be incised

and a half pint of pus was evacuated. The culture yielded hemolytic *Staphylococcus aureus*. About 4 days prior to the second admission he was seized with pain in the right chest, accompanied by a sudden rise in temperature and was re-admitted to the hospital on December 4, 1943.

On examination the physical findings in the chest were about the same as on his previous admission. Repeated blood cultures were negative, but sputum and pus from the right groin yielded *Staphylococcus aureus*. He manifested a septic temperature and developed a marked secondary anemia, associated with leukocytosis. The urine and blood chemistry findings as well as the sedimentation rates were similar to those previously reported.

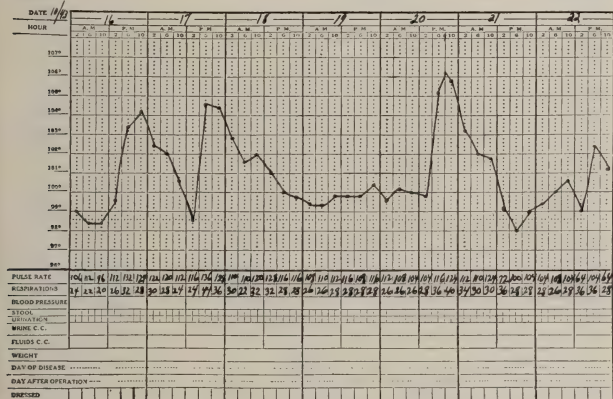
*Course:* The patient complained primarily of severe pains in the posterior aspect of the right chest which required the constant administration of morphine. After several days signs and symptoms of abscess formation at about the level of the 6th intercostal space of the right chest posteriorly became apparent. On January 18, x-ray examination revealed

### TEMPERATURE CHART BETH-EL HOSPITAL

Form 25 - 6-61 2556

TEMPERATURE RECORD B. G.

ADMISSION No. 134497



a large abscess with the fluid level at the 3rd intercostal space. This abscess emptied and refilled on several occasions. Temperature was not as septic nor did it reach the high levels attained during his first admission. He developed a marked secondary anemia with a leukocytic shift to the left. There were periods of normal temperature which coincided with the emptying of the abscess cavity.

*Treatment:* This consisted of sulfonamides throughout his second stay in the hospital, with repeated blood transfusions, and other supportive measures necessary to combat his anemia and other symptoms. On January 30 postural drainage was instituted and continued for several weeks, resulting in the emptying of the abscess on several occasions. Because of the inadequacy of this conservative therapy and the lack of satisfactory progress, the abscess was treated surgically. Although it continued to drain from one to three weeks, he was discharged on May 20, in good physical condition. On June 15 the x-ray findings showed a complete absorption of the pulmonary abscess. The diabetic state was well controlled by diet and insulin before he was discharged.

## MECHANISM OF BACTERIAL INVASION

Trauma to the skin appears to have been a definite factor in the onset of the pulmonary abscess associated with the staphylococemia in this case. The mode of invasion into the general circulation is of interest. From our knowledge of the pathology of pulmonary abscesses following such infection in similiar cases the autopsy findings may give us a clue to the *modus operandi* in this case, and may also tend to explain the latent clinical interval between the skin injury, the long involvement, and subsequent bacteremia.

Following the injury to the forearm, the patient developed an infection of the soft tissues and a local abscess. This drained into the lymphatic glands in the axilla, the infection apparently coming to a standstill at this barrier. The right axillary glands remained enlarged and tender long after the skin trauma, the local cellulitis, and the abscess had completely healed. From a study of the axillary nodes in similiar fatal cases, two modes of further extension of the infection systemically are possible.

1. There may develop an intra-lymphnodal thrombophlebitis with multiple minute embolization to the lungs by way of the subclavian vein, into which both the veins of the nodes in the right axilla and veins in the subclavian group empty.

2. Or there may have occurred intermittent, recurrent seeding of the lung with bacteria by way of the subclavian lymphatic trunk, which empties into the subclavian vein since the involved lymphnodes from the axilla drain into this lymphatic trunk.

Neither type need be associated with clinically recognizable suppuration of the lymphnodes, a finding we have noted in previous autopsies. However, when the lymphnodes suppurates and abscess is formed, our experience has been that further extension is by way of a perilymphnodal thrombophlebitis. No prolonged symptom-free interval comparable to that noted in this case generally exists.

In either of the two routes suggested, the outcome would be the formation of miliary infected infarcts in the lung. These may break down to form abscesses, ranging in size from 2 to 5 cm. The mucopurulent material from some of these small abscesses may drain into a small bronchus and eventually be expectorated. Most of them coalesce to form larger pulmonary abscesses. Entrance to the systemic circulation by the causative organisms is effected by way of the pulmonary thrombophlebitis, frequently noted histologically. These infected pulmonary veins may be immediately adjacent to the non-involved parenchyma, or within the abscess area and its zone of reactive pneumonitis. The larger the vessels involved, the more common is the systemic embolic phenomena. Septicemia, without clinical embolization occurs frequently when smaller pulmonary vessels are affected. In our case the kidney, and probably the spleen, appear to have been the seat of emboli. The interval between the initial skin injury and infection and the onset of the septicemic and embolic phenomena is probably determined by the length of time required by the offending organism to pass first, the large axillary lymphatic barrier,

and secondly the barrier interposed by the pulmonary parenchyma and the pulmonary venules as described above.



Fig. 1

9 / 19 / 43

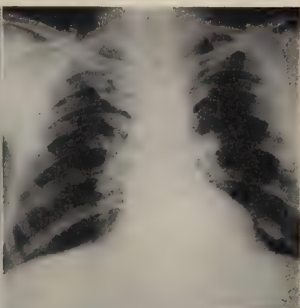


Fig. 2

9 / 23 / 43

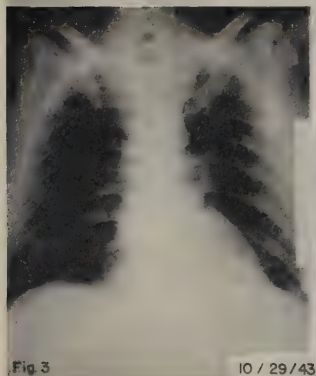


Fig. 3

10 / 29 / 43



Fig. 4

12 / 6 / 43

FIG. 1. Roentgenogram showing proliferative infiltration throughout both pulmonary fields, especially noted in the lower lobes, and an accentuation of the right interlobar fissure.

FIG. 2. Roentgenogram presenting evidence of a resolving bronchopneumonia.

FIG. 3. Roentgenograms, taken about five weeks later, at the end of the first stay in the hospital, again shows a diffused proliferative infiltration throughout both pulmonary fields.

FIG. 4. Roentgenogram taken at the beginning of the second admission shows an increase in the bronchopneumonic infiltrations with the associated involvement of the upper right lobe.

From the above analysis, it is likely that the diagnosis of bronchopneumonia made on admission was, in reality, incorrect, that the pulmonary findings on examination and by x-ray were those of miliary embolization of the lungs with

a variable amount of reactive pneumonitis. It is likely that the apparent resorption of some of the exudate noted in the serial x-ray films was due to the partial disappearance of this pneumonitis. At no time did the chest film become



Fig. 5

1 / 18 / 44



Fig. 6

2 / 9 / 44

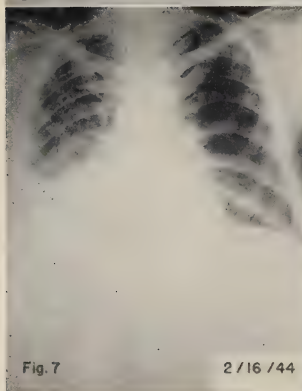


Fig. 7

2 / 16 / 44



Fig. 8

2 / 16 / 44

FIG. 5. Roentgenogram showing the presence of lung abscess with the fluid level in the 3rd interspace surmounted by air.

FIG. 6. Roentgenogram showing central absorption of the abscess with a thickened pleura.

FIGS. 7 and 8. Roentgenograms indicating refilling of the abscess with a general prominence of linear markings.

entirely clear. Similar resorption of perifocal pneumonitis is a well known phenomenon in the evolution of tuberculous lesions of the lungs.

The accompanying illustrations (figs. 1 to 8) illustrate the course of the pulmonary disease.



## COMMENTS

1. Although penicillin therapy combats an established bacteremia, it may not influence the local infection. It is therefore necessary that all foci of infection should be eradicated as far as possible.

2. It is interesting to note that in this case high fever continued despite the use of penicillin. The blood became sterile and remained so, but the temperature persisted for the next two weeks after which time it became normal.

3. The severe leukopeniac blood picture in this patient during his first admission to the hospital is interesting. Originally this was thought to be due to the use of Sulfonamides, which was apparently erroneous. Because despite the administration of large amounts of Sulfonamides for a period of several months during his second hospital admission, the patient's blood showed a persistent Leukocytosis. Therefore it seems more likely that the leukopenia was due to the infection and toxemia of the disease and not to the Sulfa therapy.

4. The relationship of infection to diabetes as a causative factor has always been a debatable question. Priscilla White (9) is of the opinion that acute infection is a negligible factor in the etiology of diabetes. She reports one hundred cases of juvenile diabetes in whom a history of acute infection was obtained in only ten per cent within the year of onset. In contrast to this view Henry J. John (10) found that twenty per cent of his juvenile cases had an infection within one or two months of the onset of the disease. Joseph H. Barach (11) also found that a large percentage of his adult cases of diabetes became manifest during an acute infection.

It has been my experience that in diabetic patients, an intercurrent infection reduces the carbohydrate tolerance in the patient observed, to one half or one third his normal tolerance.

This I believe has taken place in our patient. He showed a transient glycosuria five years ago which evidently made him a potential diabetic. The present severe infection undoubtedly had an injurious effect on the insulin producing tissues which was sufficient to break down his carbohydrate tolerance and transform him to an actual diabetic. At the present time he is receiving 45 units of Protamin Zinc Insulin daily.

## SUMMARY

Trauma of the skin may be trivial or severe, and apparently healed, when constitutional symptoms or indefinite findings in the chest develop. In the presence of acute illness with great prostration disproportionate to the physical findings, one should carefully question the patient for a possible injury to the skin or a focus of infection which may have occurred weeks or months prior to the onset of the disease.

A case is here presented in which staphylococcic pulmonary abscess developed seven weeks after an injury and infection to the forearm. The history of the injury was not obtained until a positive blood culture had been reported. The wound was apparently healed when symptoms appeared.

Roentgenologic studies are an important aid in the observance of the progress of the disease, the localization, and diagnosis. However, in the early stages of the disease, the stage of embolization, the interpretation of x-ray findings must be augmented by a careful history and a physical examination since the shadow may be indistinguishable from that of bronchopneumonia. The number of pulmonary abscesses following Staphylococcemia may be greatly increased, since more patients are recovering from the bacteremia.

I should like to express my thanks to Dr. Mendel Jacobi, pathologist to the Beth-El Hospital for his helpful suggestions in connection with the clinico-pathological phase in this case and to our roentgenologist, Dr. Maxwell Dannenberg for his aid in interpretation of the x-ray films.

#### BIBLIOGRAPHY

1. ROSENOW, E. C., AND BROWN, A. E.: Proc. Staff Meet., Mayo Clinic, 13: 89, 1938.
2. MACNEAL, W. J., AND FRISBEE, F. C.: One hundred patients with Staphylococcus septicemia receiving bacteriophage service. Am. J. M. Sc., 191: 170, 1936.
3. SKINNER, D., AND KEEFER, C. S.: Significance of bacteremia caused by *Staphylococcus aureus*. A study of one hundred and twenty-two cases and a review of the literature concerned with experimental infection in animals. Arch. Int. Med., 68: 851, 1941.
4. MENDELL, T. H.: Staphylococic septicemia. A review of thirty-five cases, with six recoveries, twenty-nine deaths and sixteen autopsies. Arch. Int. Med., 63: 1068, 1939.
5. OTTENBERG, R.: Trauma and Septicemia; Trauma and Disease. Brady and Kahn, Philadelphia, Lea & Febiger, 1937, p. 571.
6. HERRELL, W. E.: The clinical use of penicillin; an antibacterial agent of biologic origin. J. A. M. A., 124: 10, 625, 1944.
7. DAWSON, M. H., AND HOBBY, G. L.: The clinical use of penicillin, observations in 100 cases. J. A. M. A. 124: 10, 611, 1944.
8. FINKELSTEIN, L.: Reported at clinical path. conf. J. Mt. Sinai Hosp, 6: 104, 1938.
9. JOSLIN, ROOT, WHITE, AND MARBLE: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1940, pps. 452 and 671.
10. JOHN, H. J.: The diabetic child, etiologic factor. Arch. Int. Med., 8: 198, 1934.
11. BARACH, J. H.: Etiologic factors in diabetes, Arch. Int. Med. 39: 636, 1927.

## NOTES ON POLIOMYELITIS AND ITS PREVALENCE IN NEW YORK CITY DURING THE LAST FORTY YEARS

HERMAN SCHWARZ, M.D.\*

During my internship at The Mount Sinai Hospital, between the years 1899 and 1902, an occasional case was admitted to the hospital with a short indefinite history that, on awakening in the morning, the child could not walk. On examination it would be discovered that one leg was paralyzed. Curiously enough, I do not seem to remember a case where an upper extremity was involved and once in a great while an unusual condition called "Landry's Paralysis" was seen. All this was rather mysterious and in fact the entire field of acute diseases of the central nervous system, with the exception of meningitis, was an unknown terrain.

In 1905 we began to encounter many cases of meningococcus meningitis, with case after case exhibiting marked sepsis and hemorrhage. The type of infection was very new to us here. Death often occurred within 24 hours; one was able to procure a pure culture of the meningococcus from the surface of the brain and thus verify the diagnosis. A year later, an anti-meningococcus serum was produced by Dr. Jochmann in Berlin and Dr. Flexner in the United States.

In the spring of 1907, another type of acute cerebrospinal disease appeared. Case after case was brought into the Out Patient Department of The Mount Sinai Hospital with a history of a few days of fever, followed by paralysis of one or more of the extremities. The cases increased in number during the months of July and August of that year, and I visited the homes of many patients in order to learn something of the character of the onset of this disease. This took place in the summer when most of the older physicians were away and the health authorities were not aware that we were in the midst of an epidemic. Thus, I learned a great deal of the clinical picture of poliomyelitis, especially about its onset, and the findings in the cerebrospinal fluid. It was brought home to me more and more that the picture of the first few days was one of infection and could be but poorly differentiated, except by lumbar puncture, from what was at that time called "La Grippe." As is often the case during an epidemic of this sort, other diseases were mistaken for poliomyelitis; in this way much was learned about the cerebrospinal fluid in other infections. It was not uncommon to find a slight increase in the cells of the cerebrospinal fluid in cases of acute tonsillitis and particularly in acute otitis. However, an increase above 50 cells was rarely encountered unless the patient had the epidemic disease. An astounding fact learned at that time was that many so-called paralyzes cleared up with great rapidity. Whether this pseudo-paralysis was due to pain, spasm, edema of certain portions of the central nervous system or still other factors, we did not know, nor is it fully understood even at this date. The abortive cases constituted also a new syndrome at this time. They had the acute manifestations of the disease, a positive cerebrospinal fluid, but absolutely no paralyzes.

The epidemic reached its peak in the latter part of August and by October most

\*Dr. Herman Schwarz, an esteemed colleague and devoted servant of the hospital, died suddenly May 19, 1945.

of it was over. Poliomyelitis in epidemic form was rather new to us at this time, but the literature disclosed that Wickman had described a large epidemic of this disease in Sweden in 1905 which curiously enough caused little or no stir in America. While epidemics of acute poliomyelitis had occurred before all over the world, this was the first one to occur in a large city of the United States. The first epidemic of 17 cases had been described by an American physician, Colmer (whose name appeared in the literature as Colman until corrected by Medin). Another epidemic was reported by Bergenholts from Northern Sweden. He saw 18 cases occurring during the months of July to November in the year 1881. Cordier (*Tid. Skr. F. pral. med.*, 1887) reported an epidemic of 15 cases. Medin, at the Tenth International Congress in 1891 in Berlin, spoke about the epidemic possibility of the disease, describing 44 cases seen by him. In 1894, Caverly and McPhail described a small epidemic of the disease in America. Holt and Bartlett (*Am. J. M. Sc.*, 19: 647, 1908) were able to enumerate 35 epidemics in America. It was in 1905, however, that the large epidemic occurred in Sweden, which, studied by Wickman, enriched our knowledge of epidemic infantile paralysis. More than 1000 cases in the whole of Sweden occurred in that year.

In October, 1907, the importance of this subject was recognized by the New York Neurological Society, which appointed a committee to study the epidemic. This committee obtained the active support of another group appointed by the Pediatric Section of the New York Academy of Medicine. These committees decided to combine to form a larger group, which enlisted the services of Dr. Simon Flexner of the Rockefeller Institute and Dr. Charles Bolduan of the Department of Health. At the first meeting, it was decided to engage the assistance of a pathologist and an orthopedist. Accordingly, Dr. Israel Strauss and Dr. H. L. Taylor were added to the Committee. Thus, the Investigation Committee consisted of:

For the New York Neurological Society:

|                             |                        |
|-----------------------------|------------------------|
| Dr. Bernard Sachs, Chairman | Dr. J. Ramsey Hunt     |
| Dr. L. Pierce Clark         | Dr. Smith Ely Jelliffe |
| Dr. J. F. Terribery         | Dr. Israel Strauss     |

Dr. E. G. Zabriski, Secretary.

For the Pediatric Section of the New York Academy of Medicine:

Dr. Linnaeus E. La Fetra  
 Dr. Herman Schwarz  
 Dr. Louis C. Ager

For the Rockefeller Institute of Medical Research:

Dr. Simon Flexner

For the Department of Health—New York City:

Dr. Charles Bolduan

Orthopedist: Dr. H. L. Taylor

A comprehensive questionnaire was sent to the physicians of greater New York. Allowing for insufficient records and duplications, (for one must not forget that at that time the disease was not reportable), 752 cases were chosen for

careful analyses, although 2500 or more were believed to have occurred in the city. The men on the Committee were divided into sub-committees.

Sub-committee I—consisted of Drs. Bolduan, Ager and Terriberly who studied the epidemiology of the disease.

Sub-committee II—consisted of Drs. La Fetra and Schwarz who studied the prodromal symptoms of the disease and the symptoms of the period of onset.

Sub-committee III—consisted of Drs. Clark, Hunt, Jelliffe, Zabriski and Sachs who worked on the symptomatology and the course of the disease.

Sub-committee IV—consisted of Drs. Flexner and Strauss, who worked on the pathology of the disease.

Sub-committee V—consisted of Drs. La Fetra, Jelliffe, Ager, Taylor and Sachs who studied the results of the therapy used.

The findings of these various Committees were reported in a monograph published in 1907.

It was soon shown that this was an infectious disease, that symptoms of general infection were as prominent as the symptoms of paralysis, that recoveries were more common than was suspected, and that meningeal symptoms were very common in the earlier stages of the disease. Light was also thrown on the question of the relationship of poliomyelitis to acute ascending paralysis (Landry's paralysis) and to multiple neuritis.

The conclusions of the several Committees were in the main as follows:

1. The Committee on Epidemiology showed that the epidemic (and most of the other epidemics) commenced in June and usually reached its height in September, although it was noted that a few epidemics also occurred in the winter.

2. The Committee on Prodromal Symptoms found that upper respiratory infections and diarrhea or other gastro-intestinal symptoms were present. It seemed to us that the upper respiratory tract was the portal of invasion but the gastro-intestinal canal was also considered. Fever was almost invariably present, absent only in 61 of the cases studied (700). The fever lasted a few days and rarely persisted for more than seven days. The nervous symptoms noted at such time were headache, restlessness, convulsions in 51 cases, rigidity of the neck in 121 cases, pain and tenderness in various parts of the body in most of the cases. In 50 cases a skin eruption was observed. This was mostly of an erythematous nature, but macular and papular lesions were also present.

3. The Committee on Symptomatology described the clinical picture more or less as it is known now. The same forms or varieties were seen—such as:

1. Spinal Poliomyelitic Type
2. Landry's Paralysis Type (Ascending or descending Palsy)
3. Bulbar Type
4. Cerebral Encephalitic Type
5. Ataxic Type
6. Polyneuritic Type
7. Meningeal Type
8. Abortive Type

4. The Committee on Pathology was able to collect many observations on the



gross and histological features of this disease. While they were engaged in the study of the pathology of the disease in the human, Landsteiner and Popper working in Weichselbaum's Clinic in Vienna showed that the disease could be transmitted to the monkey by making an emulsion of the cord from a case of infantile paralysis, and injecting it intraperitoneally. Knoepfelmacher from the same laboratory repeated this. Strauss showed that the lesion in the animal was the same as in the human and made the further observation that the lesion in poliomyelitis was similar to that found in rabies. The intraperitoneal method of experimental transmission of the disease was not very satisfactory, failure to produce the disease being very common. Flexner then showed that injection of the virus into the brain was a sure way to bring about the disease in the monkey. This direct route produced a rather severe form of the disease in the monkey and the efforts to evaluate any form of therapy were made more difficult.

5. The report of the Committee on Therapy was particularly interesting in the light of what is being done today for this disease. It was 33 years ago when this Committee stated: "that the prolonged warm bath was the most successful element in the treatment. Every four hours the patient was put into the bath as warm as it could be borne." These baths relieved pain, promoted sleep, reduced temperature and, from work done since that time, we know it also relieved spasm. The deep hot bath was continued and furnished a medium for the better development of movement. Even at that time it was suggested that regular bathing and swimming were invaluable. It was pointed out also that care must be taken to train the child to a proper mental attitude in regard to his illness. Dr. P. William Nathan, an orthopedist of that time used to say: "get them to do as many of the movements by themselves, it is worth all of the passive exercise in the world." It was also known that partial or total recovery of the muscle power would take place after several months or perhaps a year or two.

At this point I would like to state a warning in relation to the treatment of infantile paralysis. During the first epidemic we did very little or no splinting, and this, to my mind, had resulted in many avoidable deformities. Then during the 1916 epidemic, the orthopedist entered the picture, and certainly too much splinting was done. Since then a healthy middle path has been followed.

The state of our knowledge at the end of the first major poliomyelitis epidemic was as follows: the disease was infectious; small children were more likely to become infected; it usually occurred in the summer time; although there were found many cases of more than one affected in a family, this was the exception rather than the rule. The incubation period was difficult to establish, and as far as I know, it is still difficult to establish. The spread of the disease was very poorly traced.

After this great epidemic sporadic cases were seen each year; there is no doubt that the incidence of the disease following this epidemic became greater than before. Since the early years of this century, there has been an increasingly greater area of distribution in this country and a greater incidence of the disease. Over 5000 deaths from poliomyelitis were reported by the United States Census Bureau during the years 1910 and 1915, but a conservative estimate would place the number of cases observed at about 30,000.

Then came the year 1916. During the first months of that year, even to the end of May, few cases occurred, and there was no indication that an epidemic was imminent. However, during June the cases mounted rapidly and over 27,000 cases and 6000 deaths occurred in the registration area from June to November, 1916. A report of this epidemic was published by the New York City Health Department in 1917 while Dr. Haven Emerson was Health Commissioner. On June 30th there met for the first time an Advisory Committee of the Department of Health. For the sake of the record, I append the names of this Committee.

*Advisory Council*

|                                    |                        |
|------------------------------------|------------------------|
| Dr. Louis E. Ager, <i>Chairman</i> | Dr. Herman Schwarz     |
| Dr. Elias H. Bartlett              | Dr. Rudolph F. Rabe    |
| Dr. Robert O. Brockway             | Dr. Josephine Baker    |
| Dr. Eugene S. Dalton               | Dr. J. S. Billings     |
| Dr. Thurston H. Dexter             | Dr. S. R. Blatteis     |
| Dr. George Draper                  | Dr. Charles F. Bolduan |
| Dr. Simon Flexner                  | Dr. George S. Nicholas |
| Dr. Royal S. Haynes                | Dr. W. H. Park         |
| Dr. Henry Koplik                   | Dr. B. S. Waters       |
| Dr. Howard Mason                   | Dr. R. J. Wilson       |

*Mayor's Committee on the Epidemic of Poliomyelitis*  
(To act as his advisors in the epidemic)

|                     |                      |
|---------------------|----------------------|
| Dr. E. H. Bartley   | Dr. Samuel Lambert   |
| Dr. John W. Brannon | Dr. C. H. Lavender   |
| Dr. Leland E. Cofer | Dr. Leon Luria       |
| Dr. H. B. Delatour  | Dr. Wm. H. Park      |
| Dr. A. H. Dolty     | Dr. Antonio Stella   |
| Dr. Simon Flexner   | Dr. J. M. Van Cott   |
| Dr. S. S. Goldwater | Dr. Philip Van Ingen |
| Dr. Henry Koplik    | Dr. Walter V. James  |

*Committee on Research on Polymyelitis*

|                      |                        |
|----------------------|------------------------|
| Dr. H. A. Amoss      | Dr. Josephine B. Neall |
| Dr. George Draper    | Dr. William H. Park    |
| Dr. William H. Frost | Dr. Hans Zinsser       |
| Dr. P. H. Lavender   |                        |

The total number of the cases as reported by the Health Department in the greater city was 9,023, of which 5,496 were investigated. Slightly more males were stricken than females. It seemed that at that time the colored race was less susceptible than the white race. It was thought that the small number of nursing babies affected was due to the lack of contact with other people. Yet 16 cases of nursing babies were reported who had been infected by a previous case in their respective families. There were 313 cases with two in one family; there were 28 with three in the family and six with four in the family. A special study

was made of a group of 250 cases in which more than one child was attacked. In no instance was the first child infected under six months. However, at one year of age, when a child is able to move about by its own volition, 15 children in this group were the first to be attacked.

The non-paralytic or abortive cases required special observation. This was very difficult because of mistaken diagnoses. However, of a group of 469 cases, ill at the time of the District Nurse's visit, and examined by a Health Department Physician, 25 per cent were found to be cases of true poliomyelitis. The incubation period, even in this epidemic, was difficult to establish. 584 cases fell in the category of unknown period of incubation, and 15 into a definite series where the time could be accurately determined. Eleven cases seemed to occur five days after contact, and the others within eight days. The larger number of instances with just a few days incubation were not accurate. Instances occurred in which a period of two or three weeks seemed to have elapsed.

Foods, domestic animals and insects were investigated. Of course, the article of food which came under suspicion especially was milk; it was concluded that food and milk did not play any part. Animals in the zoo did not seem to be affected. Insects could not be found to have any connection, nor could the rat be blamed.

Between the first and second epidemic, many forms of treatment were tried. Urotropin had considerable vogue because of its ability to liberate formalin in the spinal and other fluids of the body. About this time, Levaditi showed that when the spinal cord emulsion from a case of infantile paralysis was mixed with the serum from a convalescent case of infantile paralysis, the virus in the emulsion was neutralized, for on the injection of the mixture the transmission of the disease in the monkey was regularly prevented. Now at this time Dr. Abraham Zingher, an assistant of Dr. William H. Park, had been working with convalescent serum in the treatment of scarlet fever, measles and other infections. With Levaditi's experiment in mind, it was rather natural that convalescent human poliomyelitis serum be tried in the treatment of this disease. Horse serum was first used but found very irritating and possibly harmful. I was fortunate enough to have the aid of Dr. Zingher in procuring convalescent human poliomyelitis serum. We showed that it did not do any harm. But I remember the first case I used it on. This was a young man of 22 years, acutely ill with involvement of three extremities. Following the intrathecal injection there was marked increase in the neck rigidity and a tremendous number of cells were found in the cerebrospinal fluid. I thought I had caused the formation of a meningitis. However, in a few days it all cleared up, but the general course of the disease was unaffected.

Naturally, then as now, there was a great urge for some satisfactory form of treatment for this disease, and inasmuch as the neutralization experiment of Levaditi was definite, the Rockefeller Institute, under the leadership of Dr. Simon Flexner from the experimental standpoint, and Dr. Draper from the clinical point of view, began to publicize the treatment of this disease with human convalescent poliomyelitis serum. This was an instance where scientific investi-

gation was accurate, but clinical investigation was such as to mislead medical men, not only in the United States, but all over the world. A wild scramble was made to get convalescent serum from cases of recovered infantile paralysis. Furthermore, it was found that patients who had had infantile paralysis years ago had these neutralizing substances in their blood, so that from far and wide, infantile paralysis victims offered their blood for those who might become victims. This was the situation of the therapy of infantile paralysis at the end of the second great epidemic.

Dr. Josephine Neall and I had ample opportunity to judge the efficacy of convalescent serum. I had an unusual opportunity to test this serum, for in a great many cases in private practice I had to give this serum whether I wanted to or not, and on the other hand I had excellent control material in the special wards set up at this time at The Mount Sinai Hospital where no serum could be obtained even if one wanted it. Out of 100 cases and 100 controls, paralysis occurred in 43 in one group and 45 in the other group. For years, in fact from 1917 until 1931, we two had to struggle against the prevailing opinion of this form of therapy. (Arch. Ped., 3: 11, 859, November, 1916.) At many a medical meeting, I was "put on the spot." At one meeting, which I remember very distinctly, one colleague said: "any man who does not try to get convalescent serum for his patients is a criminal." Time, however, is not only a good doctor, but a great arbiter of right and wrong in all controversial subjects. It was in 1931 that Dr. William H. Park had the opportunity of testing the value of human convalescent poliomyelitis serum. That year we had a large number of cases, and it was decided to give half of the cases the serum and none to the other half. It was particularly advocated that only the pre-paralytic cases be used; 500 with serum and 500 controls were to be obtained. This was carried out with the aid of some of the younger pediatricians of whom Dr. Alfred Fisher was one. At the end of the poliomyelitis epidemic, it was clearly shown that the serum had no effect. This could have been tried before if the animal experiments had been done in the same manner as the disease occurs in the human. It is one thing to mix the convalescent serum with virus, and inject it into the animal, and another thing to give the animal an injection of the virus, wait until the very first symptoms occur and then give the convalescent serum. This was not done and the more I discussed it the more it was said that this experiment would not have any great value for the disease produced in the monkey was too severe to pass fair judgment.

During this epidemic we learned a great deal about the beginnings of the disease, the value of nuchal rigidity, the superficial abdominal reflexes, but no pathognomonic sign was discovered. Dr. Nathan Rosenthal followed the cytology of the cerebrospinal fluid hoping that it would be useful in prognosis but this was of no avail. This was the status of knowledge of infantile paralysis for a few years after the epidemic of 1916.

A striking landmark in the history of poliomyelitis was the fact that it affected the President of the United States, Franklin Delano Roosevelt. Due to his efforts, there came to be established The Warm Springs Foundation. The cli-

mate was right, the bathing was good (see our original report) and who would want a better sponsor than the Governor of the State of New York and, later, the President of the United States. Then the March of Dimes was conceived, I think by Eddie Cantor, and the President's birthday was used as an impetus for building up a fund for victims of infantile paralysis. Within a short time the Infantile Paralysis Foundation came into existence. Soon two paths were pursued by the Foundation—one relating to practical forms of therapy and education, the other in the direction of research of poliomyelitis and other virus diseases, under the guidance of Dr. Thomas Rivers.

I can not end this short history without a word about the Kenny treatment. Obviously it is not entirely new, for warm baths and compresses and voluntary movement were instituted in 1906. It is certainly not specific and, even at this time, its value is somewhat controversial. My attitude, as toward the convalescent serum, is—by all means use it for it certainly does no harm, but for Heaven's sake, do not make it appear to be the final word. I know that experts do not consider the problem to be solved, but the uninformed public thinks it is. Unfortunately we have just passed through another great epidemic. From the unbiased observations of this epidemic, our understanding of the disease will be furthered.



## THE TALCUM POWDER PROBLEM

M. G. SEELIG,<sup>1</sup> M.D., AND D. J. VERDA,<sup>2</sup> M.D.

It was late in the chapter of the development of aseptic surgery that detailed attention was paid to the hands of the surgeon and all his operating assistants. After a comparatively short period of operating with bare hands, subjected to a variety of antiseptic solutions, there came into use cotton lisle gloves as an added protective against the spores and bacteria concealed in skin crypts, hair follicles and sebaceous and sweat glands. The short step to rubber gloves was taken by Halsted. At first the rubber gloves were boiled in water, transferred to a large receptacle containing sterile water or an antiseptic solution and put on the hands under this water or an antiseptic solution. This procedure proved to be messy, due to the prolonged trickling of water down the arms and the maceration of the skin of the hands with consequent release of bacteria from cryptic skin foci. To avoid these difficulties, the so-called wet method of preparing gloves was abandoned almost universally, and was replaced by steam autoclave sterilization, talcum powder being used as an aid to the introduction of the hands into the gloves. This standard procedure, in use for more than the past third of a century, has shared with Caesar's wife the reputation of being above suspicion, until very recent times.

It is true, that there have been many reasons to question the good repute of talcum, but they, somehow or another did not register. In the first place, talcum is a silicate, and on that basis alone its virtues should have been subjected to some qualifications. All the more so since silicosis began to assume importance in clinical medicine. Then too, as far back as 1881 the noxious properties of dusting powders were emphasized. The earliest reported clinical work on intra-abdominal complications arising from powder in the peritoneal cavity had to do not with talc but with lycopodium, which is a dusting powder made from the club mosses, to the spores of which the peritoneum reacts almost exactly as it does to talc. Hippolyte Martin and later Muscatello were among the first to demonstrate experimentally the ill effects of lycopodium powder on the peritoneum. Independently, Carlo Bezzola and von Podwyssozki studied experimentally similar deleterious effects due to intraperitoneal instillation of diatomaceous earth (Kieselguhr). In 1913 Lambert showed that, even in cell growth in vitro, lycopodium spores evoked a foreign body response with outgrowth of connective tissue cells, wandering cells and giant cells. Marchand of Leipzig in 1921 corroborated experimentally the severe irritant qualities of lycopodium powder when injected intraperitoneally in animals. During the past ten years considerable experimental work has been reported emphasizing the irritant qualities of talc when injected intraperitoneally, intrapleurally, intrapericardially or subcutaneously. In fact, in a certain type of heart disease, talc has been recommended to produce pericardial adhesions in an attempt to

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promote better collateral circulation. A glance at figure 1 will make it perfectly plain why the insoluble magnesium silicate (talcum) crystals set up a severe reactionary inflammation, once they become lodged in the tissues.



FIG. 1. Talcum powder crystals,  $\times 350$ .

In 1923 Roth published the first contribution to the clinical chapter of post-operative complications arising from dusting powders. In this instance the dusting powder was lycopodium spilled from a glove which tore during a laparotomy. The results of this accident were three subsequent laparotomies for

adhesive intestinal obstructions supposedly due to tuberculosis (many miliary nodules were found on the peritoneum) until pathologic examination disclosed that the milia represented foreign body reactions to the spores of lycopodium. In 1933 Antopol reported 6 cases of complications resulting from lycopodium spores in the urinary bladder, testicle, kidney, peritoneal cavity, neck and female breast. In the same paper Antopol recorded the first case of intraperitoneal granuloma due to talc. Antopol's description of the microscopic appearance of the lesions resulting from the contamination of the peritoneum with these dusting powders was accurate and painstaking. In the instance of lycopodium, the offending agents are the lycopodium spores, whereas in the instance of talc they are the talc crystals (predominantly magnesium silicate). The spore or the talc crystal forms the center of a tubercle-like structure made up of lymphocytes, epithelioid cells and giant cells (of both foreign body and tumor giant cell types). We might add, based on our experiments, that these tubercle-like structures rarely show any central necrosis, although central caseation necrosis may occur. Neither the macroscopic nor the microscopic anatomy of these lesions is as important as are the end results of their formation, namely a fibrosis which produces intraperitoneal adhesions. In our experimental animals, we found all types of adhesions, ranging from a massive occlusion of almost the entire peritoneal cavity to less massive localized adhesions of stomach, spleen, liver and omentum or intestinal loops, or merely thin adhesive bands of fixed omental strands that not infrequently caused death from intestinal obstruction in our animals.

Our interest in the talcum powder problem rests on a dual basis. In the first place, a relative was seriously compromised by a talc peritonitis with repeated intestinal obstruction following a simple appendectomy, and in the second place, as the problem is coming more and more to the attention of the clinicians and pathologists, more and more contributions are appearing in medical literature. For example, there have been published numerous case histories of patients who have been subjected to from two to four and even more operations for the relief of intestinal obstruction caused by abdominal silicosis (talcum peritonitis). Such cases have been reported by Antopol, Feinberg, Owen, Byron, Ramsey, German, Byron and Welch, Ramsey and Douglass, and McCormick and Ramsey.

The noxious properties of talc are thrown into bolder relief when one learns that it is a trouble maker elsewhere than in the peritoneal cavity. Granulomas resulting from talc implantation have been described in the rectum, vagina, cervix and brain and in healing wounds by Antopol and Robbins, Erb, Antopol, Fienberg, Ramsey and Douglass, Grieco, Cline and others. We have heard, by way of a personal report, of troublesome consequences following the accidental entrance of talcum powder into the conjunctival sacs of operating room nursing personnel. On the basis of a study of the talcum hazard in the preparation of rubber gloves for sterilization, made by the Illinois Division of Industrial Hygiene, Kronenberg suggests it would be wise to institute measures to control and remove talc dust in order to avoid health risk to nurses. An-

other peculiarly interesting aspect of the problem lies in the fact that in all this literature there is no suggestion of a suitable substitute for talcum and no clear cut insistence that talcum must be done away with in surgery.

In the last analysis, however, our major concern with talcum powder has to do with the abdominal lesions and complications resultant from its introduction into the peritoneal cavity. There is more than gentle irony in the fact that we have been overlooking a prime offender, at the same time that we have been expending much thought and energy on the prophylaxis of post-operative intraperitoneal adhesions due to agencies much less vicious than is talcum.

There are three principal sources from which talcum may gain entrance into the body:—

1. From the surface of powdered gloves. It is unfortunately true that many surgeons do not attempt to wash their gloves in a sterile solution before operating, and it is, unhappily, more true that those who do take this precaution, can never succeed in getting rid of all the talcum which verily sticketh closer to rubber than a brother.

2. From the surface of instruments and from sterile gauze, towels and other things that come in contact with the operative field. This hazard does not seem to have been mentioned before in surgical literature. If one will place a dark object in the operating room while the surgical team dusts hands with talcum, preparatory to donning gloves, it may be readily demonstrated that the surface of the dark object will be overlaid by a thin layer of talcum if time enough is allowed for the powder to settle. We consider this contamination of instruments and surgical supplies as a very real hazard.

3. The talcum may escape through rents accidentally made in the gloves during the performance of operations. Such accidents furnish a fertile source of contamination with talcum, because the fingertip of a carelessly prepared glove often contains as much as 100 mg. of tale. Studies by Weed and Groves show that (a) in 74.4 per cent of all operations some gloves are torn and (b) 22.6 per cent of all gloves used show rents or punctures. These data were obtained by Weed and Groves through a period of twenty months of operating using a total number of 35,763 gloves. Some months 32 per cent of the gloves showed rents or punctures. The high incidence of perforation of rubber gloves during operation (22 per cent) was recently emphasized in an editorial in the *British Journal of Surgery*. German found that in a series of 50 patients 40 showed intraperitoneal tale that had been deposited accidentally during a previous laparotomy. German examined his microscopic preparations in polarized light, which renders the tale crystals much more readily visible. We show in figures 2 and 3, the striking difference between tale crystals as demonstrated in an intraperitoneal granuloma viewed by ordinary and by polarized light. In 42 of German's patients (84 per cent) one previous laparotomy, in 7 patients (14 per cent) two previous laparotomies, and in 1 patient (2 per cent) five previous laparotomies had been performed. Of course in such a study the tale may come from the surface of the gloves or through accidental perforations of them, or possibly from gauze sponges or pads contaminated with talcum powder.

Any attempt to find a substitute for talc must be based on two fundamental considerations: 1. The substitute powder must possess such a degree of actual or potential solubility as to be disposed of rapidly and completely by some form of peritoneal or tissue absorption. If this is not true, the powder collects in the peritoneal cavity as masses or plaques which induce foreign body granulomas, which in turn result in adhesions; or the powder sets up foreign body reaction in wounds or on mucous membranes. 2. The powder must possess such a



FIG. 2. Talcum powder crystals ( $\times 116$ ) seen in a post-operative intraperitoneal granuloma under ordinary light.

degree of insolubility as to withstand steam sterilization without losing that dusting property which serves to prevent the glove surfaces from adhering.

In our initial search for a substitute for talcum, we devoted much time to experimentation with prepared chalk (calcium carbonate) because it has been used for years as a face powder and because Miller and Sayers (who used powdered limestone) have shown that when injected into the peritoneal cavities of experimental animals it is eventually absorbed without any consequent ill effects. However, when we injected it into our animals we found that although it was absorbed eventually (five to six weeks) it nevertheless, during the early period



following injection, induced granulomas and peritoneal adhesions. In time these granulomas tended to disappear and the adhesions to thin out, but we could demonstrate some menacing intraperitoneal adhesions and strands eight weeks after injection.

After failure with calcium carbonate powder we turned our attention to corn starch as a promising substitute for talc because of its admirable dusting quality and its appealing smoothness. Furthermore, there were rational reasons for assuming that it would be taken care of by the diastatic action of the peritoneal

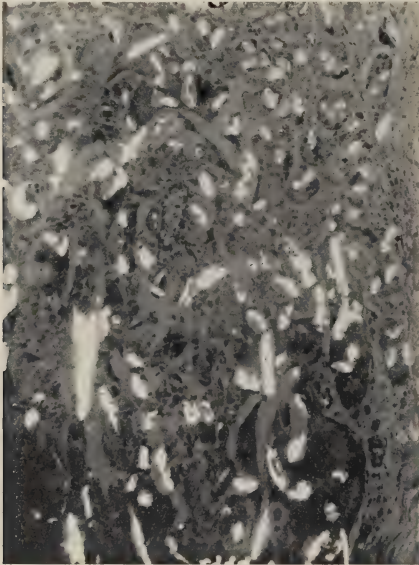


FIG. 3. Talcum powder crystals ( $\times 116$ ) seen in a post-operative intraperitoneal granuloma under polarized light. (Same section as shown in Fig. 2.)

fluid and thus be rendered safely absorbable. These assumptions were borne out by our animal experiments, which demonstrated that rats would dispose of an intraperitoneal dose of starch comparable to  $1\frac{1}{2}$  pounds (0.68 kg.) injected into a human being of average weight (150 pounds, or 68 kg.). The animals, within twelve to twenty-four hours after intraperitoneal injections of starch, showed complete absorption of 3 cc. of a 10 per cent suspension without a vestige of any kind of local or general undesirable affect. These findings are in contrast to the demonstrated chemotactic effect of starch recorded by Chamber

and Grand and Kile. This discrepancy is probably due to the fact that in our experiments the starch was injected into the peritoneal cavity, whereas the other investigators made their injections into the subcutaneous tissue. We encountered much difficulty however in the fact that, when we attempted to sterilize starch powdered rubber gloves by autoclaving, the starch gelatinized on the glove surfaces, causing them to adhere and the whole glove to stiffen and glaze. There is reason to believe that it may be possible to develop a special starch powder that will not gelatinize during steam sterilization. This is a consummation devoutly to be wished. Indeed, at this writing, it seems that it has been attained; because the Research Laboratories of the Corn Products Refining Company have developed for us, a special starch dusting powder, manufactured by the application of new processes recently developed by them. This starch is not yet in production and the current difficulties with equipment priorities may preclude production until after the war. The special process inhibits the tendency of starch to swell in hot water, thereby rendering it possible to subject gloves to steam sterilization without any gelatinization and consequent stickiness and adhesive effects. There is every reason to assume that this new special Starch Dusting Powder bids fair to solve the vexatiously serious talcum powder hazard. We have subjected it both to laboratory and operating room tests and have found it to measure up to all requirements.

Before the Corn Product Refining Company developed this Special Starch Dusting Powder we had found that Potassium bitartrate fulfilled all the requirements of a dusting powder for rubber gloves. This powder is sufficiently insoluble (0.37 gm. per hundred cubic centimeters of water at 0°C. and 6.1 gm. per hundred cubic centimeters at 100°C.) to preserve its powdering effect after autoclaving. Studies of the pharmacologic action of the tartrates in man and experimental animals by Underhill and his co-workers, Salant and his co-workers, Post and others reveal that only large doses are toxic. It has been shown that the toxic dose in the experimental animal is 0.5 gm. per kilogram of body weight administered subcutaneously, or about  $1\frac{1}{4}$  ounces (35 gm.) in a man weighing 150 pounds. Our studies show that in a carelessly powdered glove as much as 100 mg. of powder may collect in each fingertip. Assume for the sake of argument that gloves have been carelessly prepared and that during an operation ten finger ends were torn, spilling the maximum amount (1,000 mg.) of potassium bitartrate in the peritoneal cavity, there then would have been scattered only one thirty-fifth of the toxic dose. One does not have to worry about the bitartrate powder on the surface of the gloves, because, unlike talc, it washes off easily and completely before operation.

At the time that we did our early work on potassium bitartrate we reported that it tended to shorten the life of the gloves. We also got the impression, after the publication of our first paper, that after gloves had been sterilized several times with potassium bitartrate, they tended to become flaccid and sticky. Since that time however, one of the extensive manufacturers of rubber gloves instituted a detailed set of experiments, that were well controlled and that showed that the bitartrate powder had no tendency to cause stickiness,

and that it had no influence on either the ordinary life or on the tensile strength of the gloves. We confirmed these statements after substituting a brand of gloves other than those we had used in our original experiments.

#### MATERIALS, METHODS AND RESULTS

We studied twenty-four different powders: calcium carbonate (precipitated), calcium gluconate, calcium citrate, calcium phosphate (dibasic), calcium phosphate (tribasic), calcium tartrate, calcium d-malate, magnesium bicarbonate, magnesium carbonate, mag-

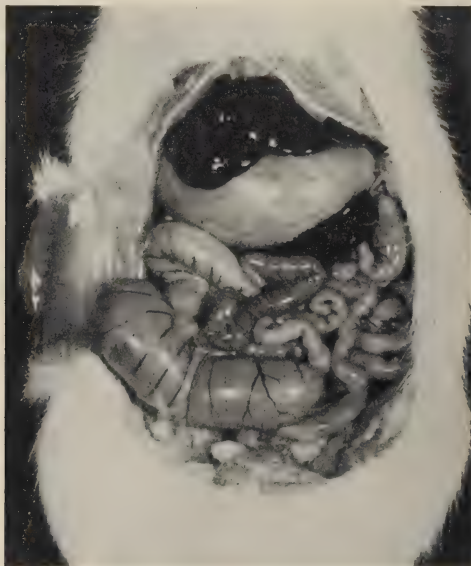


Fig. 4. Peritoneal cavity of a normal rat. White flecks are high lights.

nesium phosphate (dibasic), magnesium-ammonium-phosphate, magnesium tartrate, potassium bicarbonate, sodium bicarbonate, sulfanilamide, talcum and potassium bitartrate. Seven different forms of starches were also tried: cornstarch, arrowroot starch, soluble starch, rice starch, Linit starch, and amylocellulose. These studies were directed toward determining primarily whether or not the various powders possessed such dusting properties as to permit the gloves to come out of the process of steam (autoclave) sterilization in adequate condition. Many of the powders we tried met this test successfully because most of them were soluble. With the starches, however, we were baffled by the gelatinization which resulted from sterilization and rendered the gloves unusable. As stated earlier, we believe that the Corn Products Refining Company have now solved the perplexing starch problem.

The second step consisted in testing the physically satisfactory powders on white rats (150 to 350 gm. in weight) by injecting sterile watery suspensions of varying concentrations (usually 2 cc. of 5 per cent solution) into the peritoneal cavities. We made in all 194 experiments on 194 individual rats. At intervals varying from five minutes to twenty-four weeks after injection the rats were killed, autopsies performed and gross and microscopic studies made of pathologic lesions.

The results of the experiments may be summarized very briefly by saying that, with one exception, every powder that successfully met the test of steam sterilization produced pathologic lesions of one type or another in the peritoneal cavities of the test animals, i.e., powder plaques, granulomas, adhesions or peritoneal serous exudates (fig. 4 and 5). The



FIG. 5. Peritoneal cavity of a 300 gm. rat, 5 days after injection into it of 2 cc. sterile suspension of 5 per cent talcum in water. Arrows X and Y mark adhesions, plaques and granulomata.

one exception was potassium bitartrate, which whether it was strewed on the abdominal viscera through a laparotomy wound or injected into the peritoneal cavity as a watery suspension in varying strength, was rapidly disposed of without causing even the slightest untoward toxic or physical effects, local or general, in any of our experimental animals. Since there is no certain information as to how potassium bitartrate is disposed of after its entrance into the peritoneal cavity, we are making a special but so far inconclusive study of this point. However, we are assured by our work both of its rapid absorption and of the absence of any symptoms of toxicity with appropriate dosage.

It is a notable fact that potassium bitartrate of a mesh of from 210 to 270 seems to powder gloves better than does the finer mesh powder. We therefore recommend the coarser mesh (210-270), which in reality is the commercial product (cream of tartar) even though it feels

a trifling bit more gritty to the hands of the surgeon. When the standard technic for rubber glove sterilization was followed (subjecting the powder, either in gauze sachets or in metal or glass shakers, and subjecting likewise the powdered gloves to 15 pounds of steam pressure for fifteen minutes) the results were, in every way satisfactory. In this connection it is important to remember that in contrast to talc with its heavy bacterial and spore content the bitartrate is actually bacteriostatic and relatively innocuous, from the point of infectivity, even before sterilization.



FIG. 6. Bacteriostasis caused by potassium bitartrate placed on agar culture of colon bacillus.

In attempting to determine the effect of potassium bitartrate on pyogenic bacteria, agar plates were seeded by pouring an evenly dispersed broth suspension of staphylococci (*Staphylococcus aureus*) and *Escherichia coli* over the plate surface. A loopful of potassium bitartrate was transferred to one or several evenly distributed points on the seeded agar surface. Within twenty-four hours the staphylococci and *E. coli* had grown sufficiently to make it possible to evaluate the results of the experiments. The organisms studied the agar surface except in those small areas where the potassium bitartrate was planted. A clear zone 1.5 cm. in diameter free of all growth surrounded the potassium bitartrate. The ability of the potassium bitartrate to inhibit the growth of the bacteria, namely, bacteriostasis, is apparently accomplished by raising the hydrogen ion concentration (lowering



the pH) of the agar at the bitartrate site. No surgeon will fail to grasp and appreciate the undoubted clinical value of the phenomenon of bacteriostasis. Figures 6 and 7 demonstrate the bacteriostatic property of potassium bitartrate on staphylococci and *E. coli* cultures.

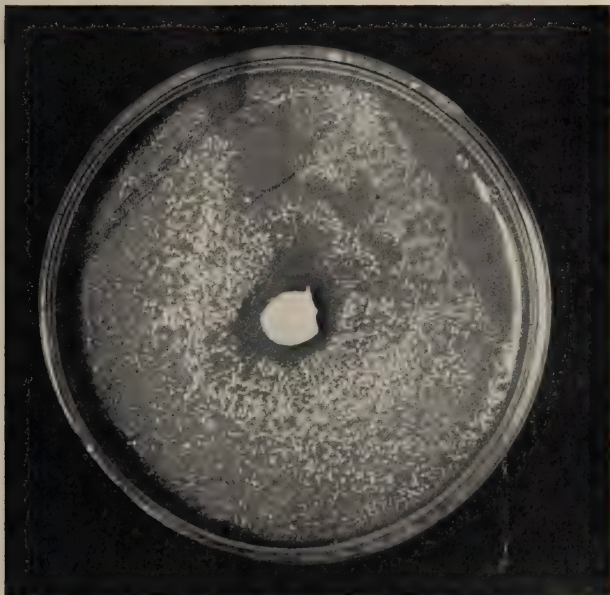


FIG. 7. Bacteriostasis caused by potassium bitartrate placed on an agar culture of staphylococcus aureus.

#### CONCLUSIONS

1. Talcum powder is, under any circumstance, a grave menace in surgery. Once having gained entrance into the animal organism, this powder sets up a reactionary, productive inflammation that is permanent and progressive and that may be provocative of almost insuperable complications. Furthermore, postoperative residual talcum has been demonstrated by one investigator in various intra-abdominal viscera in 80 per cent of patients he examined.
2. It is certain that even meticulous care in washing off the surface of rubber gloves before operating does not guarantee against contamination of the operative field with talc.
3. The difficulty in substituting for talc lies in the fact that an insoluble powder like talc (hydrous magnesium silicate) sets up a granulomatous foreign body

reaction, whereas a soluble dusting powder dissolves during the process of sterilization of the gloves, rendering them adherent and thus difficult or impossible to put on. Dry sterilization of the gloves might be regarded as a solution of this difficulty, but it does not meet the rigid requirements of aseptic surgery and is highly destructive to the life of the gloves. Boiled gloves are sloppy and generally undesirable.

4. Potassium bitartrate meets the physical requirements imposed by steam sterilization. It is readily and harmlessly disposed of by the body tissues and fluids. It causes no consequent peritoneal adhesions. Since, therefore, there are no demonstrable risks attendant on its use, it may be recommended as a substitute for talc in powdering rubber gloves. We have received no complaints regarding undesirable skin effects.

5. Potassium bitartrate possesses a certain degree of bacteriostasis for the colon bacillus and *Staphylococcus aureus*.

6. It is important that in the process of sterilization the potassium bitartrate should be subjected only to the now standard and accepted technic for sterilizing rubber gloves, namely fifteen minutes of autoclaving under 15 pounds of steam pressure.<sup>3</sup>

7. There is every reason to believe that, in a short time, there will be on the market a non-gelatinizing starch powder that will prove more satisfactory than is potassium bitartrate.

<sup>3</sup> A complete bibliography on the role of talcum in surgery is appended to a paper published by us in the *J. A. M. A.*, 123:950 (Dec. 11), 1943.

# AN EVALUATION OF THE CLINICAL APPLICATIONS OF THE VAGINAL SMEAR METHOD<sup>1</sup>

EPHRAIM SHORR, M.D.

## INTRODUCTION

It is axiomatic that progress in any field of medicine is usually proportional to the existence of objective criteria and the availability of specific therapeutic agents. During the past two decades there has been a gratifying development in both respects in the field of female sex physiology. Chemical research has provided potent hormonal agents concerned with ovarian activity and there has been developed a variety of histological, biological and chemical criteria for evaluating the various phases of menstrual function.

In spite of this progress, the present status of the diagnosis and management of disturbances of female sex physiology remains far from satisfactory, a situation to which a number of factors contribute. A major obstacle is, without doubt, the difficulties inherent in the problems encountered and their limited susceptibility of correction by methods now available. However, some measure of responsibility for our present inadequacies can be laid to the failure to use the available diagnostic and therapeutic procedures to greatest advantage. In a field which is developing rapidly, some lag is inevitable between the development and the widespread utilization of technical procedures and therapeutic agents. In the present instance, this lag has been unusually great, due in part to the fact that many of the helpful diagnostic measures are so expensive, cumbersome and technically exacting as to sharply limit their use. These drawbacks are shared by such valuable procedures as urinary assays for gonadotrophins, estrogens and progesterone excretion products, and the endometrial biopsy; and there is no present indication that these deterrents to their more widespread use will be eliminated in the near future.

For these reasons, this clinic somewhat over a decade ago, undertook an investigation of the possible usefulness of the vaginal smear technic introduced by Papanicalaou as a method for evaluating both normal and pathological ovarian function and as a guide to therapy. This method had many obvious advantages; it was simple, inexpensive, non-traumatizing, and permitted a continuous rather than an episodic observation of ovarian function. The smear could be prepared, stained and evaluated within a few minutes, thus eliminating the delay associated with all other methods. It remained to be determined, however, just how specific was the information provided by the vaginal smear and how this information might provide a basis for the recognition of abnormalities of ovarian function, and guide their management. To this end, studies were carried out in collaboration with Papanicalaou (6, 8-10, 13), Cohen, De

<sup>1</sup> From the New York Hospital and the Department of Medicine, Cornell University Medical College.

These studies were carried out under a grant from the Josiah Macy, Jr. Foundation.

Allende and Hartman (5) on women with normal and pathological ovarian function. Other experiments were designed to reveal the specific cytological changes induced in the vaginal secretions by the several hormones participating in the ovarian cycle (6, 7, 8).

It is the purpose of this paper to review briefly the results of these studies and to evaluate the usefulness of this technic for the diagnosis and management of disturbances in sex physiology. As might be expected, the method was found to share certain limitations with all other present methods of observing ovarian function; hence it is most ideally used in conjunction with other procedures such as urinary hormonal assays and endometrial biopsies, so as to obtain as complete a picture as is possible at the present time. Nevertheless, when used as the sole method of study, provided its limitations are understood, it can furnish an extremely satisfactory qualitative and quantitative picture of ovarian function and serve as a sensitive guide for the most efficient use of the therapeutic agents now available. It has been possible to so simplify the technics involved as to permit it to become an office procedure. The cytological criteria for the evaluation of the vaginal smear picture have been quite securely established by a number of published studies. It is beyond the scope of this paper to deal with this subject in much detail. It will have served its purpose, should it encourage a more extensive use of a method which, by virtue of its simplicity and its many other advantages, appears to be the procedure most adaptable to widespread clinical uses as a guide to the diagnosis and management of disturbances in female sex physiology.

#### METHOD

Since the information provided by the vaginal smear is histological in character, the proper use of this method is dependent upon adequate fixation of the secretions, and the utilization of specific staining methods capable of revealing cellular detail. The recognition of the necessity for proper fixation was a major contribution of Papanicolaou and resulted in his fundamental contribution to the subject (4) where others had failed. During recent years, several very satisfactory and specific staining procedures have been developed in this and in other laboratories, which have provided criteria for the recognition and differentiation of significant cell types. It has also been possible to greatly simplify staining procedures and yet retain the desirable differential characteristics of the more complicated staining methods. A single differential stain has been devised which has so simplified the technic that it can be made an office procedure. The method of obtaining the vaginal smear and using the single differential stain is described below:

The vaginal smear is aspirated by means of a glass pipette to which is attached a strong-walled rubber bulb of about 1 oz. capacity. The pipette should be made of stout-walled glass tubing with an external diameter of about one-quarter inch. Six inches is a convenient length and the bore should be constricted at the tip to an opening of about 1.5 mm. A slight bend near the tip facilitates insertion into the vagina. The pipette should be thoroughly dried before using, since contamination of the vaginal secretion with water may distort the cells. With the bulb compressed, the pipette is inserted gently to a distance of about three inches into the vaginal vault. The bulb is then released and the pipette slowly withdrawn. The aspirated secretion is then expelled onto a clean glass slide with two or three forcible compressions of the bulb and the slide immediately fixed for one or two minutes (or longer if desired) in a solution of equal parts of ether and 95 per cent alcohol. It is essential to fix the slide while the secretion is moist since drying

alters the staining reaction sufficiently to make the interpretation of the smear completely unreliable. If more than one smear is to be placed in the bottle of fixative, it is desirable to attach a metal paper clip to the slide at the opposite end to the smear to prevent contact of the slides which might rub off the secretion.

Occasionally, the secretion is so scant and the resulting smear so thin that it is almost impossible to avoid drying without special precautions. The following method has proved effective for this purpose and indeed, may be generally adopted, since it permits smears of proper thinness to be made without the necessity for undue haste. A drop of solution of equal parts of glycerine and 95 per cent alcohol is placed on the slide and spread out over an area one-quarter inch in diameter. The secretion is then expelled directly onto this area and mixed with the glycerine-alcohol before fixation. When the vaginal secretion is scant, it is frequently advantageous to suck up the glycerine-alcohol mixture into the pipette for a distance of two inches, expelling the excess beyond that coating the walls. The vaginal smear is then obtained in the usual manner and expressed onto the slide. With both techniques, a minimum of dry smears is obtained and there is enough time to make the thin type of smear which is best for observing histological detail. The presence of blood in the vaginal secretion tends to obscure the cytological details. This interference can be eliminated by the use of a 10 per cent solution of acetic acid in the alcohol:ether mixture described above. This serves to lake the red blood cells during fixation. A thin smear of the bloody vaginal secretion is placed in this solution for 5 minutes and then transferred to the standard alcohol:ether mixture until stained. These slides should be stained for 5 instead of 2 minutes (see below). Patients can be taught to take their own smears at home, the slides being kept in the fixative until the series is complete. The metal clips should be removed after the slides have been in the fixative for 24 hours to avoid rust formation which will alter the staining characteristics of the smear.

The smears can be stained by a variety of methods (1, 2, 3) some of which are more suitable for the laboratory, and others simple enough to be readily carried out in the office. For the latter purpose the following single differential stain<sup>2</sup> has proved extremely satisfactory (2):

|                                    |           |
|------------------------------------|-----------|
| Ethyl alcohol (50%) .....          | 100 cc.   |
| Biebrich Scarlet (water sol.)..... | 0.3 gm.   |
| Orange G.....                      | 0.100 gm. |
| Aniline blue (water sol.).....     | 0.025 gm. |
| Fast Green FCF.....                | 0.075 gm. |
| Phosphotungstic acid, c.p.....     | 0.25 gm.  |
| Phosphomolybdic acid, c.p.....     | 0.25 gm.  |
| Glacial acetic acid.....           | 1.0 cc.   |

After fixation the slide is placed in the staining solution for approximately two minutes. After allowing the excess stain to drain back into the original bottle, the slide is dipped ten times in 80 per cent and 95 per cent alcohol. It is next either dipped ten times in absolute alcohol if this is available, or gently blotted dry with filter paper; and then dipped ten to twenty times in xylol to complete dehydration. Dehydration is generally complete if the xylol runs off the smear in a smooth sheet. Particular care to insure dehydration must be exercised in damp weather. It is then mounted in damar with a cover slip to make a permanent preparation, which it is convenient to label with name and date by means of a glass marking pencil. This single differential stain provides a sharp differentiation of cornified and non-cornified elements with good nuclear staining, as well as satisfactory staining of all the significant elements in the smear, such as leucocytes, erythrocytes, sperm, trichomonas, bacteria and mucus. Cornified cells take on a brilliant orange-red coloration; non-cornified elements assume a bluish-green hue of varying shades and intensities. It should

<sup>2</sup> This Single Differential Stain can be obtained from Wyeth Inc., 1600 Arch St., Philadelphia, 3, Pa.



be pointed out that the excess of red dye is often not completely removed from the thick portions of the smear; hence these areas should be disregarded and observations confined to the thinner portions of the smear.

#### THE BASIS FOR THE USE OF THE VAGINAL SMEAR AS A METHOD FOR STUDYING OVARIAN FUNCTION

The vaginal epithelium shares with the endometrium the property of having its structure specifically influenced by the ovarian hormones. It possesses a three-zone structure which alters in characteristic fashion with the changing pattern of the ovarian hormones elaborated during the menstrual cycle. These changes are reflected in the cells which are being constantly shed into the vaginal cavity. The influence of the individual hormones, that is, the estrogens and progesterone, can be differentiated by observations on the menopausal castrate. In this way, the cytological changes specifically due to the estrogenic hormones (6) can be recognized both with respect to the structure of the vaginal epithelium and the vaginal secretion which results from its desquamation. The cytological effects resulting from the combined action of estrogens and progesterone during the second half of the menstrual cycle are likewise reproducible in the menopausal castrate (7). The vaginal smear may therefore be regarded as a method of bioassay of the ovarian secretions in the particular patient under study or treatment, and as such would seem to possess advantages over the usual methods of bioassay by which the end products of the metabolism of the ovarian hormones are first extracted from urine as in the case of estrogens, then injected into rats or mice and evaluated on the basis of vaginal smear changes in the injected animal.

The validity of this substitution for the animal bioassay, of a bioassay directly on the subject under study will rest on the accuracy and specificity of these cytological indices in the human. A strong case has already been made for the specificity of the cellular changes occurring in the human as a result of the action of estrogens whether elaborated by the ovary or exogenous. The increasing production of estrogen shown by bioassays to occur during the first half of the cycle and to culminate in the ripening of the follicle midmenstrually, is paralleled by the expected changes in the growth of the cells and degree of cornification exhibited. In the menopausal subject increasing doses of administered estrogen are accompanied by progressive increases in cornification. The specificity and quantitative aspects of the combined influence of estrogens and progesterone during the second half of the cycle is on somewhat less secure grounds, due in large measure to the more complicated cytological picture seen under these circumstances. Nevertheless, with experience accurate evaluations of the normality of the luteal phase can be made as judged from concurrent endometrial biopsies. It is anticipated that further work in this direction will provide additional cytological criteria which will make more certain the evaluation of the luteal phase.

#### A PROGRAM OF STUDY

Familiarity with the cytology of the vaginal smear is most readily acquired by starting with the simpler staining techniques and selecting for study the simpler

cytological reactions. It is helpful from the outset to set up certain methodological criteria and to adhere to them in the evaluation of the vaginal smear picture. One should systematically make a note of the following characteristics:

- 1) The size and shape of the epithelial cells and their staining properties.
- 2) The size and shape of the nuclei and the details of their structure.
- 3) The extent of cellular desquamation.
- 4) The distribution of the cells whether discrete or in clumps.
- 5) The amount and character of the accompanying mucus.
- 6) The extent and character of the leucocytosis.
- 7) The degree of cellular destruction as indicated by free nuclei.
- 8) The presence of endometrial cells.
- 9) The presence of red cells, either well preserved or shadow forms, and fibrin.
- 10) The bacterial content.

Certain factors complicating the interpretation of the smear should also be borne in mind. Thus cervical erosions or endocervicitis will produce a persistent leucocytosis, and trichomonas will cause irritative phenomena distorting the usual cytological picture. Trichomonas can with practice be recognized in the staining preparations and should be suspected when particularly smudgy smears are encountered which are rich in leucocytes and contain many relatively small cornified cells with large nuclei predominating, instead of the usual small pyknotic nucleus of the cornified cell, and with considerable perinuclear vacuolization. The classification of the different cell types found in the vaginal secretion should then be made following the criteria already described in publications from this laboratory. The investigator should then make a collection of a number of series of vaginal smears which will serve as standards of reference.

The simplest type of reaction is that exhibited by an amenorrheic or menopausal subject with an atrophic type of smear in whom estrus is induced by the administration of an estrogenic hormone. The atrophic smear which is characterized by a predominance of small, round or oval cells with large well-preserved nuclei, the "deep" cells of Papanicolaou and Shorr, will undergo a progressive series of changes which reflect the influence of the estrogen on the development of the initially atrophic vaginal epithelium to the typical three-layered type characteristic of the mid-menstruum. This epithelial transformation is accompanied by the desquamation of progressively more mature cells which become larger, more quadrilateral in shape, and thinner and flatter. The nuclei at first large and well-preserved, become smaller and undergo degenerative condensation. At full estrus the vaginal smear is dominated by large flat discrete cells with cornified cytoplasm staining red, and a small pyknotic nucleus. Following the cessation of estrogenic therapy, a series of regressive changes occur with a gradual return to the original state. Once familiar with these changes, the clinician is in a position to deal with estrogenic replacement therapy in amenorrhea and to employ the smear in the management of the menopausal syndrome. He will also be reasonably qualified to distinguish the several types of amenorrhea and to recognize certain types of anovulatory cycles.

He may then proceed to the more difficult question of evaluating the normality

of menstrual cycles. This will be facilitated by the collection of a series of slides covering a whole menstrual cycle from patients of proved fertility. The reliable evaluation of the normality of the luteal phase comes only after considerable study, although extreme deviations from the normal may be readily appreciated. A study of the differences between the passive regression of the vaginal smear picture after an induced estrus in a menopausal castrate, and the vaginal smear picture following the ovulatory peak of the normal menstrual cycle will provide considerable help in the evaluation of the normal cycle. The following system of dividing the menstrual cycle into its significant episodes is favored by the writer (5):

A. The menstrual phase—this is the breakdown phase during which desquamation usually involves the entire functionalis and part of the intermediate zone. This generally lasts 4-5 days.

B. The postmenstrual phase (5-8 days)—during which there is a gradual change in the epithelium and vaginal smear under the influence of the growing follicle.

C. The preovulatory phase (2-3 days)—this is characterized by a sudden spurt of estrogenic activity accompanied in the smear by striking and usually progressive increase in the percentage of cornified cells and a gradual clearing of the smear.

D. The ovulatory peak (generally 1 day)—which is the expression of the height of follicular development just prior to ovulation. The secretion is thin, clear and leucopenic. There is a predominance of thin, wafer-like cornified cells with small, pyknotic nuclei.

E. The postovulatory reaction (generally 1 day)—this is the surest available guide for determining the time of ovulation. The better the cycle the sharper are the cytological changes, which consist of leucocytosis, clumping, folding and curling of the cells, and generally, a reduction in the cornified elements.

F. The luteal phase (10-14 days)—may be divided into the early luteal phase lasting 3-4 days during which considerable cornification is likely to persist due to the shedding of the upper cornified layers previously built up under the influence of the estrogenic hormone; and late luteal phase which is the expression of the increased growth and desquamation of the luteal epithelium resulting from the combined action of estrogen and progesterone. The smear is rich in cells, which are usually present in thick clumps imbedded in a thick mucoid secretion. Cornified cells are significantly reduced in number and the non-cornified elements present a variety of shapes and sizes with small nuclei predominating. The average size of the non-cornified cells during this phase is somewhat smaller than the non-cornified cells of the estrogenic phase of the cycle. They frequently show a characteristic type of folding with sharp edges.

G. Premenstrual phase (1-3 days)—this smear is a reflection of the waning hormonal production and is generally thinner, less rich in cells which are less likely to clump and are somewhat larger and flatter than during the luteal phase and contain somewhat larger nuclei. There may be a moderate increase in cornified cells, and erythrocytes may be present.

Figure 1 is illustrative of the cytological changes occurring in the menstrual cycle of a patient of proved fertility. The reader will find in the appended bibliography a number of studies which may be consulted for fuller details of the cytology of vaginal smears in normal and pathological states.

Changes in the Vaginal Smear  
Picture During a Normal Ovulatory Cycle

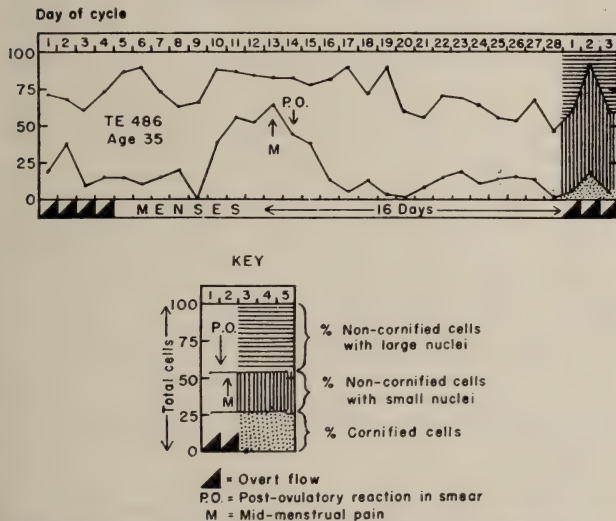


FIG. 1. This graph represents the cellular changes seen during a normal ovulatory cycle. The classification was based on an evaluation of 200 epithelial cells in each smear. Menstrual phase, days 1-4; postmenstrual phase, days 5-9; preovulatory phase, days 10-12; ovulatory peak, day 13; postovulatory reaction, day 14; early luteal phase, days 15-16; late luteal phase, days 17-27; premenstrual phase, day 28. (From DeAllende, Shorr and Hartman (5).)

THE APPLICATION OF THE VAGINAL SMEAR METHOD TO THE MANAGEMENT OF  
AMENORRHEA

The amenorrheas are customarily classified into two major groups: the term "primary" amenorrhea is applied to subjects who have never overtly menstruated; amenorrhea arising after the initiation of menstruation is designated as "secondary." This classification is unsatisfactory and incomplete, since it provides no information as to the factors responsible for the amenorrhea, whether ovarian or pituitary, and fails to employ available objective criteria for discriminating between varieties of amenorrhea in both groups.

Amenorrhea may arise from the failure of the anterior pituitary to provide either rhythmic or adequate amounts of gonadotrophic stimulation to ovaries capable of normal response, or from ovarian defects either of congenital origin or due to pathological changes occurring at any time post-natally.

In both instances, the degree and character of the derangements may vary greatly. Any adequate therapeutic program should be based on an awareness of all these factors. Apart from the actual inspection of the organs involved, which is generally feasible only with the ovaries except when x-ray evidence of pituitary disease is present, the most informative objective criteria are provided by assays of urinary gonadotrophins and a study of the vaginal cycle. The information derived from the study of the urinary gonadotrophins is at present largely quantitative in character and serves to establish their presence or absence. Thus, a high urinary titre of gonadotrophins in amenorrhea would strongly suggest a failure of ovarian response, a circumstance frequently reported in certain types of "primary" amenorrhea for which genetic ovarian defects are responsible. Grossly subnormal gonadotrophin excretion would suggest pituitary deficiency without however throwing any light on the factors responsible for this inadequacy, that is, whether nutritional states, emotional stress, pathological changes in the pituitary, or specific inhibitions in pituitary function due to hormonal disturbances resulting, for example, from arrhenoblastomas or adrenal cortical adenomas.

By means of serial studies of the vaginal secretion it has been possible to recognize at least four distinct types of amenorrhea. Since the vaginal smear can only reflect the changing patterns of ovarian hormone production, it can provide only indirect evidence of pituitary gonadotrophin elaboration; hence, the analysis of the vaginal smear type should, wherever possible, be reinforced by the estimation of pituitary gonadotrophin excretion to obtain a more complete picture.

The following description of the distinctive vaginal smear types found in amenorrhea is based on a previous report (8) and supplemented by additional information derived from my subsequent study of approximately 100 cases in the Endocrine Clinic of the New York Hospital.

*A. The atrophic, acyclic type:* This is characterized by a uniformly atrophic smear in which the predominance of deep cells indicates virtual absence of estrogenic hormone production. Most cases of "primary" amenorrhea exhibit this type of smear. Many excrete normal or excessive amounts of pituitary gonadotrophins warranting the inference, frequently supported by laparotomy, that a developmental ovarian anomaly underlies this syndrome. Other cases appear to be of pituitary origin. The *atrophic, acyclic* smear also occurs in "secondary" amenorrhea, and in these cases is generally indicative of a profound depression of pituitary gonadotrophic activity. It is very usual in the syndrome of anorexia nervosa with amenorrhea. It is frequently present in amenorrhea secondary to arrhenoblastoma, virilizing tumors of the adrenal cortex and Cushing's syndrome due to adrenal cortical adenoma, disturbances in which there is an excessive elaboration of steroidal hormones capable of inhibiting pituitary gonadotrophic function. It is also seen in the menopause.



The prognosis as regards initiation of normal ovarian function in patients with this type of smear picture varies with the underlying condition. Where congenital ovarian or pituitary defects are responsible it is virtually hopeless. In instances where the delay in the onset of pituitary gonadotrophic function may have been due, for example, to a previously poorly controlled juvenile diabetes or to hypothyroidism, the amenorrhea may respond to the correction of these defects. In "secondary" amenorrhea, this type of smear picture has a variable prognosis though, as a rule, the expectation of spontaneous resumption of menstruation is not good, and worsens in proportion to the duration of the amenorrhea. In long-standing anorexia nervosa with *atrophic acyclic* smears, the amenorrhea may be permanent despite an improved nutritional and psychological state. However, we have observed such cases spontaneously resume normal menstruation; hence the prognosis although not good, should be guarded.

*B. The subfunctional acyclic type:* This group exhibits a variety of vaginal smear pictures having, however, two characteristics in common; they do not vary significantly from day to day, and they all reveal appreciable ovarian insufficiency. The cells are further advanced in development over the deep cells characteristic of the atrophic smear, and may approach the mature squamous non-cornified cell. They are generally smaller, however, and large undegenerated nuclei predominate. There is frequently considerable cytolysis, free nuclei and bacteria. Cornified cells are conspicuously absent or rare. These smears are counterparts of the types predominating during the menopause, although occasionally smears are encountered similar to those found in the luteal phase of the menstrual cycle.

This type of smear is characteristically seen in "secondary" amenorrhea. It indicates subnormal rather than absent ovarian function and presupposes some pituitary gonadotrophic activity, subnormal in amount and acyclic in character. It is obviously necessary to rule out the existence of pathological ovarian changes which might make the ovary incapable of responding to pituitary stimulation; but most of the cases appear to be on a functional basis and associated with pituitary hypofunction. The prognosis for spontaneous resumption of menstruation appears to be much better in "secondary" amenorrhea of this type than in those cases with *atrophic, acyclic* smears.

*C. The subfunctional cyclic type:* In contrast with the preceding types, this group presents a fluctuating type of vaginal smear picture with recurring episodes of cyclic ovarian activity resulting in significant estrogenic hormone production and a high degree of cornification in the vaginal smear. These periods of cornification usually last from 1-2 weeks and are followed by rapid regressions to smear types indicative of low estrogen production. These episodes of ovarian activity may occur at fairly regular intervals or may be widely spaced. In the regressive phase immediately following the peak of cornification, red blood cells are occasionally present in the vaginal secretion, a circumstance comparable to the postovulatory bleeding not infrequently seen during regular menstrual cycles. The regressive stage differs in cytology from the luteal phase of the normal cycle, hence these episodes probably represent periods of anovula-

tory ovarian activity which have not been prolonged or intense enough to produce endometrial changes sufficient to result in withdrawal bleeding. The responsibility for this anovulatory type of response may reside in the ovary or originate in the absence of the luteinizing component of the pituitary gonadotrophins. A third, though undoubtedly much less common cause for the failure to bleed may be the failure of the uterus to respond to the ovarian hormones, as in the case cited below. Cycles of this type are occasionally encountered in the natural menopause and after hysterectomy; and when they occur in the presence of a menopausal syndrome, they are accompanied by spontaneous symptomatic relief. The existence of such a cycle in a woman of 36 with primary amenorrhea provided the explanation for her normal secondary sexual characteristics, the absence of menstruation being due to congenital atresia of the uterus.

This type of amenorrhea is, with few exceptions, limited to the "secondary" group. It should, however, be suspected when there is a significant development of secondary sexual characteristics in "primary" amenorrhea. The differentiation between "primary" amenorrhea due to ovarian or pituitary defects and to delayed puberty can frequently be made by the recognition of subfunctional cyclic ovarian activity in the vaginal smear, since ovarian activity of this character often precedes the menarche by many months. The prognosis for spontaneous resumption of menstruation by patients exhibiting this type of smear picture is quite good, particularly if the cycles occur regularly; however, I have observed instances of this type of amenorrhea to persist for several years without the initiation of menstruation.

*D. The hyperfunctional acyclic type:* This is the least common type and, in my experience, has been confined to the "secondary" amenorrheas. It has been encountered almost exclusively in patients with a history of menorrhagia, and generally interrupts, for varying lengths of time, such bleeding episodes. Amenorrheas of this type have been seen to persist for as long as six months. The vaginal smear uniformly shows a significant degree of cornification, with no luteal transitions throughout the period of amenorrhea. Such reductions in cornification as occur from time to time are brief and not very marked; they are apparently insufficient in degree or duration to produce bleeding of the withdrawal type. Eventually, this sustained estrogenic hormone production, presumably from a persistent functional follicle or series of follicles, is terminated by a bleeding episode from a hyperplastic endometrium. A similar vaginal smear picture is occasionally seen in the menopause, when the uterus has been removed but the ovaries or ovarian remnants remain. One such patient remained in almost constant estrus for approximately two years.

The significance of this type of amenorrhea lies in its inevitable production of endometrial hyperplasia and its consequences.

This classification of amenorrheas by vaginal smear types can, either alone, or supplemented by urinary gonadotrophic hormone assays, provide a valuable guide to therapy. Our present therapeutic measures are of three types (1) general or correctional, (2) stimulative, and (3) substitutional. The first aims to overcome metabolic and psychological disturbances or to correct specific ab-

normalities such as virilizing tumors, hypothyroidism, etc., which may underlie the failure of pituitary gonadotrophic activity. The second procedure attempts to stimulate ovarian activity by administration of gonadotrophic principles derived from the anterior pituitary, from pregnant mare serum or from the urine of pregnant women. (It is also in a larger sense substitutional as well, since it functions in the place of a dormant pituitary.) The third consists in the administration of estrogenic and progestational hormones, alone or in combination, to replace the deficiencies in endogenous production resulting from ovarian failure.

When *general or specific correctional measures* are employed, their effects on ovarian function can be readily evaluated by means of the vaginal smear. Changes in ovarian activity can be detected well in advance of overt menstruation. Furthermore, once menstrual regularity becomes established, the experienced observer should be able to determine the normality of the newly established menstrual cycles. In a subject with an atrophic acyclic type of secondary amenorrhea due to an arrhenoblastoma, definite resumption of ovarian activity was evident in the vaginal smears ten days after the removal of the tumor, and the second menstrual cycle followed the resumption of menstruation and had the characteristics of a normal ovulatory cycle.

*Stimulative therapy* with gonadotrophins is admittedly unreliable. The circumstances underlying the variability of response to this group of hormones must be complex. An important determining factor may be the variable susceptibility to gonadotrophic hormones of the different types of amenorrheas described above. A second factor responsible for some failures may be the absence of adequate criteria for estimating individual dosage requirements. The induction of bleeding is an unreliable index, since it overlooks partial responses to inadequate dosage in a potentially susceptible subject and also provides no information as to the quality of the ovarian response, whether ovulatory or anovulatory, which led to the bleeding. Both of these uncertainties can be resolved by the aid of the vaginal smear (8, 12). Furthermore, the choice of the more suitable gonadotrophin, whether follicle stimulating or luteinizing, and the proper timing of the treatment should be aided by knowledge of the type of spontaneous ovarian activity exhibited by the subject. This holds particularly for the subfunctional cyclic type of amenorrhea, whose vaginal smear picture warrants the interpretation that the ovary is responding to the follicle stimulating but not to the luteinizing component of the pituitary secretion, and would suggest the use of the latter type of gonadotrophin at the height of the follicular response.

At present, *substitutional therapy* is the more generally employed for the management of amenorrhea. It consists in the cyclic administration of estrogens alone or in combination with progesterone in such a way as to simulate the concentrations and time relationships in which these hormones are produced during the normal menstrual cycle. This is done with the reasonable expectation that the effects of the ovarian hormones on the uterus and other secondary sex structures will be reproduced in a cyclic manner similar to that occurring during

a normal menstrual cycle, and with the hope, frequently not realized, that this type of therapy will eventually induce spontaneous pituitary-ovarian cyclic activity which, once initiated, will continue. Whatever the limitations of this type of therapy, it is more likely of success if adequate replacement is achieved. Unfortunately no clearcut recommendations can be made as to dosage requirements for estrogenic hormones which will hold for every patient, nor can reliance be placed on withdrawal bleeding as proof that full replacement has been attained. It would be convenient indeed, if a unit of dosage could be selected which would provide full replacement in patients where the induction of estrus

### Range of Dosage Required for Estrus in the Human

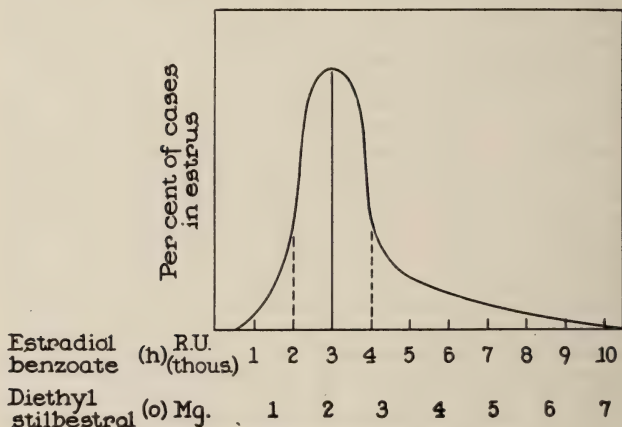


FIG. 2. Range of dosage required for estrus in the human.

is our goal; but this is unfortunately not the case. Human requirements vary just as greatly as they do in animals. Hence, it is necessary to ascertain the dosage requirements for the individual patient. This variability in response to estrogens is illustrated in figure 2 showing the approximate distribution curve in the human arrived at by means of the vaginal smear. Differences of as much as 1,000 per cent can exist between individual patients as to the requirement of estrogen for the induction of estrus. The employment of a uniform dosage for all patients is, therefore uneconomical, since it is wasteful when excessive and ineffective for those requiring larger amounts of hormone.

The problem of the individual dosage requirements for induction of estrus is further complicated by the availability of a wide variety of estrogenic hormones

both natural and synthetic for administration by various routes. The multiplicity of units—international, rat and milligrams—adds to the confusion. The vaginal smear provides the simplest method of ascertaining the relative potencies of these hormones by the various routes by which they are given (13). The method of using the vaginal smear for this purpose is illustrated in figure 3 in which the relative estrogenic potencies of three such compounds is arrived at by comparison of their ability to induce vaginal cornification.

When it is decided to employ cyclic replacement therapy with estrogenic hormones in a case of amenorrhea, it is our practice to administer the hormone for two weeks of each month in those amounts which will induce estrus. Under

Relative Potency of Synthetic Estrogens in the Human as Measured by the Vaginal Smear

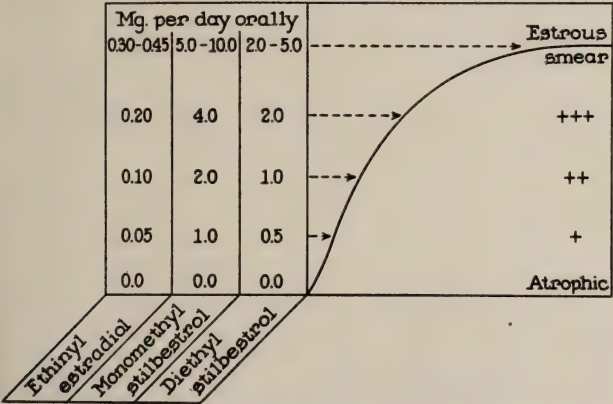


FIG. 3. Relative potency of synthetic estrogens in the human as measured by the vaginal smear.

these circumstances, withdrawal bleeding will usually occur approximately five days after interruption of medication. This regime is then repeated, starting on the same day of each month, for as long as may be deemed desirable, with periods of interruption to allow for determining whether there is evidence of the looked-for resumption of spontaneous ovarian activity. For one type of amenorrhea, at any rate, that due to primary ovarian or pituitary defects, the success of this regime in developing adequate secondary sexual characteristics is unquestioned.

When more complete replacement therapy is employed, utilizing in addition, progesterone intramuscularly or its oral equivalent, anhydro-hydroxy-progesterone, the progestational hormone is usually administered for a period of 5-7 days after the induction of estrus, either alone or in conjunction with estrogens.



The use of this more complete regime of replacement therapy as compared with the reliance on estrogen alone shares with the latter method the same uncertainty as regards permanent benefit. The vaginal smear at present appears to offer no help in estimating the amount of progesterone which should be administered. It is generally assumed that a dose of 10 mg. of progesterone intramuscularly daily is approximately equivalent to the amount elaborated daily during the luteal phase of a normal cycle. Our experience would indicate that when anhydrohydroxy-progesterone is employed by mouth, the dosage should be ten times as great.

Progesterone or its oral equivalent can also be used alone to induce withdrawal bleeding in certain cases of amenorrhea. Since progesterone cannot stimulate the endometrium in the absence of estrogen, only those cases are suitable for this type of treatment which are already producing sufficient endogenous estrogen to act synergistically with the administered progesterone to induce endometrial growth. These cases can be most readily selected by means of vaginal smear studies which can also provide information for the subfunctional cyclic type, as to the most appropriate time for the administration of the hormone.

It is beyond the scope of this paper to deal in greater detail with the therapeutic problems presented by amenorrhea. Their all too brief treatment had as its purpose merely to point out the many ways in which the use of the vaginal smear will permit their more controlled management.

#### THE VAGINAL SMEAR IN THE MANAGEMENT OF THE MENOPAUSE

One of the earliest applications of the vaginal smear method was its use in the management of the menopausal syndrome (6, 11). The prevailing vaginal smear types at the menopause while presenting considerable variation, almost always indicate the presence of significant ovarian insufficiency, except for the relatively rare episodes of spontaneous ovarian activity described above which are accompanied by temporary spontaneous symptomatic relief. The administration of adequate amounts of estrogen transforms the smear to the estrus type, with the amelioration of the menopausal symptoms. For details of the cytological characteristics of the menopausal smear and its alterations under the influence of estrogen, the reader is referred to the study by Papanicolaou and the writer.

Many misconceptions have existed as to the rationale for the use of the vaginal smear in the conduct of the therapy of the menopausal syndrome. In the first place, no symptomatic evaluations can be made on the basis of the smear since the menopausal smear is characteristic of all subjects in the menopause whether or not the menopausal syndrome exists. The function of the control smear is merely to serve as a base line for evaluating the therapeutic progress and permit the correlation between the degree of symptomatic relief and the level of replacement therapy necessary to achieve comfort. Since symptomatic relief and not the induction of estrus is the goal, very many patients can be adequately managed by subjective criteria without the employment of the vaginal smear. However, this index provides much valuable information which can contribute to the physician's understanding of the menopausal syndrome and the individual

patient under study, and has other advantages which recommend its use. Among these, is the opportunity to evaluate the relative potency of the wide variety of estrogenic agents now available by different routes of administration, and the aid it provides for ascertaining whether or not any particular sign or symptom occurring in a patient suspected of the menopausal syndrome is actually specifically related to the estrogenic deficiency of that period.

It has already been pointed out in a previous section that there is no unit of dosage applicable to all patients, and that one patient may require ten times the amount of hormone needed by another to produce the same biological and

### Relation of Vaginal Smear Changes to Symptomatic Effects of Estrogens

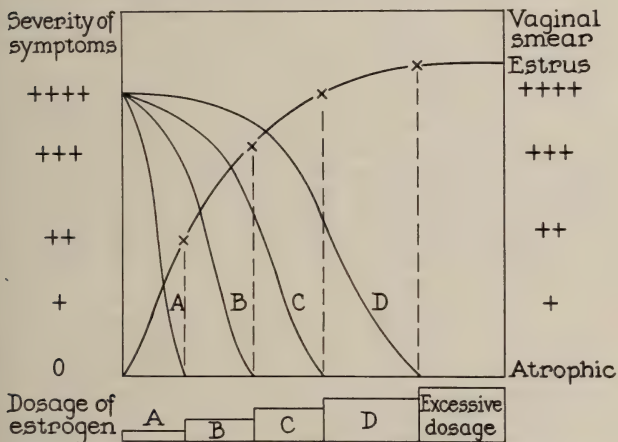


FIG. 4. Relation of vaginal smear changes to symptomatic effects of estrogens.

symptomatic effect. These individual differences in response may cloud the treatment of the menopausal syndrome. Symptoms may persist to a significant degree, for example, with doses ordinarily deemed adequate to abolish discomfort. These inadequate responses generally arise either because of insufficient dosage or because of the fact that the symptoms have another origin. The vaginal smear is useful in resolving these problems. If significant symptoms persist in the presence of an estrus smear and hence with full replacement therapy, it is safe to regard such symptoms as not part of the menopausal syndrome but of a different nature. When failure to relieve symptoms is due to inadequate dosage the vaginal smear provides the simplest method of insuring that the dosage requirements of the individual patient are met.

Finally, attention may be called to certain inferences which can be made from the correlation of the vaginal smear, that is, the biological response, and the degree of symptomatic relief experienced. The following diagram illustrates the variability of this correlation. Patients may be divided into those who obtain symptomatic relief with minimal smear changes, that is with minimal degrees of replacement therapy and those who require more and more complete replacement, up to full estrus to alleviate their discomfort. It has been our experience that the prognosis in terms of tempo of readjustment to the menopausal state is inversely proportional to the degree of replacement therapy needed for symptomatic relief as revealed by the vaginal smear. It has also been our experience that those patients with the most profound psychoneurotic elements participating in the genesis of their menopausal syndrome are most likely to fall into the group requiring the greatest degree of replacement therapy. It is also helpful to be able to follow, by means of the vaginal smear, the progress or lack of progress in the readjustment process by noting changes in the degree of replacement therapy required in the course of treatment.

Substitution of exactitude for rule-of-thumb methods in the treatment of the complicated menopausal picture not only provides for the most economical method of dealing with this syndrome but enriches the physician's understanding of it. The vaginal smear changes which occur in the menopause following the administration of estrogenic hormone are among the simplest from the histological point of view and should present little difficulty to anyone with even a moderate histological experience. Even those who might find the study of the cycle in menstruating women a rather formidable task will be gratified by the ease with which the changes from the initial picture of ovarian insufficiency to that of estrus can be recognized.

#### THE VAGINAL SMEAR IN INFERTILITY AND MENORRHAGIA

The utilization of the vaginal smear method in the management of the more complex disturbances of menstrual function, such as infertility, and the metrorrhagias, requires, as a rule, more experience than is necessary for its use in the menopause and in amenorrhea. This is particularly true in the case of infertility, due to the difficulties inherent in this problem and to the present uncertainties as to the variations in the vaginal smear picture compatible with normal menstrual function. The menorrhagias present somewhat less difficulty, and tend to follow more readily recognizable patterns. Both of these conditions will be briefly discussed in the light of the information which can be derived at present from their study by this method.

A) *Infertility of functional origin:* Daily smears throughout one or two consecutive cycles should be available for study, utilizing the criteria previously set up for evaluating the normality of the different phases of the cycle. These cases usually fall into two major groups. In the first, unmistakable evidence is present of such gross abnormalities of ovarian function as to warrant the positive diagnosis of anovulatory cycles. Three such types of cycles are most frequently encountered. All may be associated with menstrual periods occurring regularly and at normal intervals, although some degree of irregularity is somewhat more

usual. The first is characterized by a uniform vaginal smear picture throughout the cycle, with cytological characteristics indicative of gross ovarian insufficiency (5). The second type of anovulatory cycle simulates the picture seen in an atrophic acyclic amenorrhagic subject, in whom estrus has been induced by the administration of an estrogen followed by a sharp regression to the original atrophic smear on the cessation of treatment, and by withdrawal bleeding. The bleeding and postmenstrual phases in these patients (5) are usually marked by the presence of many deep cells. There then follows a rapid, striking increase in cornified cells, which may comprise as much as 70–80 per cent of the epithelial cells in the smear. After reaching this peak, the vaginal smear regresses within one or two weeks, occasionally even more rapidly, to the atrophic type, and bleeding of the withdrawal type occurs. The inference made from this vaginal smear pattern is that follicular growth has taken place with abundant estrogen production, but without subsequent luteal transformation. The third variety of anovulatory cycle is marked by a persistently high degree of cornification throughout the cycle, with no signs of a postovulatory reaction or a luteal phase. This type is frequently associated with excessive bleeding, and will be discussed in more detail below.

Unfortunately, these are not the most usual types of cycles seen in patients with sterility presumably of functional origin. It is more common to see borderline cases which one cannot with certainty designate as normal or subnormal and for whose evaluation every additional type of information—endometrial biopsies, temperature curves, urinary assays for pregnandiol excretion, etc.—is necessary. Some infertile patients will present extremely normal vaginal smear cycles as well as secretory endometrial biopsies. Occasionally discrepancies exist between the vaginal smear picture and the endometrial biopsy, the latter indicating secretory activity, the former, significant deviations from the normal pattern. When this occurs in an infertile patient, it is at present difficult to decide which index is the more reliable. This decision will eventually rest on the accuracy with which the luteal phase can be evaluated quantitatively on the basis of the histology of the endometrium, and on the reliability of the assumption that the presence of progesterone invariably indicates that ovulation has taken place.

When the infertility is due to the male partner, and artificial insemination is decided upon, the vaginal smear permits the selection of the most appropriate time for insemination, which should take place within a day or two of the ovulatory peak. It is helpful to analyze the cycle previous to the one selected for insemination, so as to determine beforehand the approximate date of ovulation, as well as to familiarize oneself with the pattern characteristic of the patient. This will increase the accuracy with which the subsequent ovulatory peak is selected. Calculation of the date of ovulation is often misleading, since this may fluctuate by several days in successive cycles. This has, of course, been repeatedly emphasized in relation to the “rhythm” type of contraceptive control. The utilization of the vaginal smear should reduce the number of inseminations necessary.

B) *Meno- and metrorrhagia*: These present some of the most difficult problems

to deal with, both from the standpoint of diagnosis and management. In all such cases, it is a primary responsibility of the physician to rule out pathological factors as causative agents. The usefulness of the vaginal smear for the purpose of diagnosing neoplasms of the genital tract was pointed out by Papanicolaou, who first detected the presence of cancer cells in the vaginal smear. This work was subsequently amplified by Papanicolaou and Traut (15), and by Meigs, Graham, Fremont-Smith, Kapnick and Rawson (16). This aspect of the vaginal smear method, while of particular interest to the gynecologist, also merits the attention of the clinician who would, by its use, be less likely to overlook a neoplasm of the genital tract in patients under treatment for supposedly functional disturbances.

What is said here relates solely to bleedings of a functional character. They are very variable in their manifestations and in their significance, both as regards well-being and menstrual function. Some of those occurring most commonly will be discussed briefly, chiefly with respect to what the vaginal smear can reveal as to their etiology and suggest by way of therapy.

Midmenstrual bleeding is not an uncommon occurrence. When it is on a functional basis, it is almost always associated with the postovulatory reaction. It may be overt or only detectable in the vaginal smear. This type of bleeding may possibly result from a temporary failure to sustain endometrial integrity due to a delay in the elaboration of progesterone, after the peak of endometrial proliferation has been reached at ovulation and the usual postovulatory reduction in estrogenic hormone production has occurred. This type of postovulatory bleeding is also occasionally seen in subfunctional cyclic amenorrheas, and during the menopause at periods when spontaneous subfunctional ovarian activity occurs. When patients present this type of bleeding during their period of menstrual activity, the possibility of some type of ovarian dysfunction should be suspected, and is not infrequently revealed by studies of their vaginal smear cycle.

Another type of bleeding, frequently microscopic but occasionally overt, is seen during the menopause and in some cases of amenorrhea. This bleeding is associated with extremely atrophic vaginal smears and apparently arises from a similar atrophic condition of the endometrium. In these cases, extreme care should be taken in studying the vaginal smear to rule out the possibility of bleeding originating from a neoplasm. This type of bleeding is usually abolished by the administration of estrogenic hormone.

More common and distressing are the debilitating menorrhagias which occur throughout the period of menstrual activity and have a high incidence during early adolescence and in the climacteric. Endometrial biopsies almost invariably indicate some degree of endometrial hyperplasia, but fail to provide specific information as to the factors responsible for the hyperplasia. It has been possible to differentiate, by vaginal smear studies, two major types of ovarian functional disturbances which lead to hyperplasia and menorrhagia.

In the first type, the vaginal secretions present the characteristic picture of significant ovarian insufficiency with absent or negligible cyclic ovarian activity.



The smears are generally very uniform throughout the cycle and fail to reveal a distinct ovulatory peak. Cycles of this character are associated with menorrhagias at every age period; they are responsible for an overwhelming majority of the functional bleedings of adolescence and the climacteric, a correlation which would be anticipated from the prevalence of ovarian insufficiency at these periods. Just how an hyperplastic endometrium develops as a result of chronic ovarian insufficiency remains a matter of speculation. A cumulative growth of the endometrium might take place through sustained estrogenic activity, even though of a low order, if desquamation should be incomplete at menstruation. This failure of the endometrium to shed completely may arise from the absence of the abrupt reduction in ovarian hormone concentration which occurs premenstrually and during menstruation in the normal cycle. Although this sharp reduction in hormonal content is probably not the only factor responsible for the breakdown of the endometrium at menstruation, it is without doubt a major one. The withdrawal bleeding which occurs when hormonal support is withdrawn from an induced proliferative or secretory endometrium is generally interpreted as supporting this inference. If this assumption is correct, it should be possible to build up an hyperplastic endometrium over a period of months of subnormal cycles.

This hypothesis provides a rational basis for the treatment of menorrhagia associated with this type of vaginal cycle. It would suggest the enhancement of endometrial development by the premenstrual administration of ovarian hormones, followed by an abrupt discontinuation of therapy two or three days before the expected flow. The withdrawal of hormonal support from well-developed epithelium should result in a more complete breakdown and a more normal menstrual flow. Its subsequent regeneration should then take place from the same histological baseline which is characteristic of the normal menstrual endometrium. This is essentially what is accomplished by a curettage. The premenstrual enhancement of endometrial development can be accomplished by means of estrogens, progesterone, or a combination of both types of hormones. All three regimes have been found capable of controlling this type of menorrhagia; however, the use of progesterone alone, or in combination with estrogens, is more physiological and generally more reliable. It has been possible to restore normal bleeding at regular intervals for long periods of time to patients with this type of menorrhagia. The continued study of the vaginal smear will not infrequently reveal spontaneous alterations of ovarian function indicative of a more normal type of cycle, at which time further treatment becomes unnecessary. During adolescence, this regime, by bridging the gap between these anovulatory cycles and the normal ovarian activity which comes with sexual maturity, can obviate the necessity for more drastic measures.

The prolongation of the period of bleeding in this type of menorrhagia also awaits explanation. Its duration may be dependent to some measure on the slow restoration of the denuded epithelium due to a delay in the production of the amounts of estrogen necessary for its regeneration. Some support for this suggestion is provided by the frequency with which the duration and amount of

bleeding can be curtailed by the administration of estrogens during the menstrual phase.

The second major type of menorrhagia is most commonly met with in the third and fourth decades. Its endometrial picture cannot be differentiated from that of the previous type, but the vaginal cytology reveals an entirely different causal mechanism. It is characterized by sustained and excessive estrogen production, and an absence of evidence of luteal activity. It may, therefore, be termed the *hyperfunctional* type, as opposed to the *hypofunctional* type described above. The bleeding episodes are often associated with transient brief reductions in the extent of cornification, a circumstance which may be responsible for the initiation of the bleeding since it indicates a corresponding reduction in estrogen concentration below that previously sustaining the endometrium. This type of anovulatory cycle with persistent estrogenic hormone production, may be associated with an amenorrhea of several months' duration which terminates in a prolonged bleeding episode; or the periods of menorrhagia may occur with a fair degree of regularity. The basis for this type of menorrhagia appears to be the persistence of a functional follicle or series of follicles which fail to undergo luteal transformation.

The most reliable present form of treatment is ameliorative in character and based on the same principles which underlie the treatment of the hypofunctional type. It consists of the premenstrual induction of a well-developed secretory endometrium by the administration of adequate amounts of progesterone or its oral equivalent, and the interruption of therapy two to three days before the expected flow. The effects of the progesterone are readily recognized in the vaginal smear. This regime usually results in regular menstruation of normal character and duration. It is necessary to continue treatment until the vaginal smear indicates that a more normal type of ovarian activity is taking place, at which time it may be safely discontinued.

#### VAGINAL SMEARS IN THE USE OF ANDROGENIC HORMONES

The androgenic hormones have been shown capable of suppressing menstrual function in the human. Their action is two-fold. In proper concentrations they are able to neutralize the peripheral effects of the estrogens on the endometrium and vaginal epithelium (9). Their second effect is the suppression of the gonadotrophic activity of the pituitary. Both of these effects are of practical importance in the management of certain menstrual disturbances. The use of these hormones is most effectively controlled by vaginal smear studies. When androgenic hormone therapy is initiated midmenstrually, a typical sequence of events occurs (10); the appearance of the next menstrual period is accelerated by several days and it is likely to be scantier than usual. By this time, the neutralizing effects of the androgens on the vaginal epithelium are usually apparent in the smears. With the continuation of treatment for an additional two weeks, the vaginal smear rapidly assumes an atrophic picture indicating that complete neutralization of estrogens has been achieved, and that the amounts of hormone given are sufficient to inhibit pituitary gonadotrophic activity. If treatment is

stopped at this point, the next menstrual flow will be delayed and will usually take place about a month after the last injection. The interference with pituitary function is therefore temporary.

These effects of the androgens on menstruation provide the basis for their use in therapy; and this can be safely done provided excessive dosage and prolonged treatment is avoided, since these hormones are capable of inducing masculinizing effects of which one, the lowering of the voice, may be irreversible. It is frequently used when it is deemed desirable to interrupt a specific episode of menorrhagia; although once this has been achieved, reliance should thereafter be placed on the more physiological methods described above.

Androgens are also frequently useful in the management of endometriosis, particularly in young, inoperable cases where sterilization is undesirable. The basis for this therapeutic measure is the fortunate tendency of ectopic endometrial implants to poorly survive the involution which can be achieved by the androgenic hormones. The same criteria described above for the use of the vaginal smear in the control of the use of androgens in menorrhagia is applicable to the treatment of endometriosis.

#### SUMMARY

The results have been summarized of a ten-year experience with the vaginal smear as a diagnostic procedure and a therapeutic guide for the management of a variety of problems arising from disturbances in female sex physiology. This method is not advocated as an exclusive approach to any of these problems but should ideally be correlated with other diagnostic aids such as the endometrial biopsy and assays of the urinary hormones arising from pituitary and ovarian activity. In contrast with most other methods for evaluating ovarian function, the vaginal smear is much more accessible to the clinician. It has the further advantage of cheapness, simplicity and of permitting a continuous rather than an episodic study of ovarian function. The methodology has been simplified so that it may be carried out as an office procedure. A variety of disturbances in female sex physiology have been described in the management of which the value of the vaginal smear can be considered quite reasonably established. Some of its applications such as in the menopause and in the amenorrheas require a cytological background and experience no greater than that which the physician can readily acquire. Those which involve an evaluation of the normality of the menstrual cycle require more serious study. Such a study will be rewarding and will greatly enhance the understanding of the complex phenomena involved in normal and pathological ovarian activity to those willing to undertake it. Furthermore, it presents a ripe field for further investigation.

#### BIBLIOGRAPHY

From the extensive literature on this subject, a few references have been selected which can serve as a basis for the initiation of the study of the vaginal smear.

##### A. Staining technics:

1. SHORR, E.: A new technic for staining vaginal smears. II. *Science*, 91: 579, 1940.

2. SHORR, E.: A new technic for staining vaginal smears. III. A single differential stain. *Science*, 94: 545, 1941.
3. PAPANICALAOU, G. N.: A new procedure for staining vaginal smears. *Science*, 95: 438, 1942.
- B. Cytology of normal and pathological menstrual cycles:*
4. PAPANICALAOU, G. N.: The sexual cycle in the human female as revealed by vaginal smears. *Am. J. Anat.*, 52: 519, 1933.
5. DEALLENDE, I. L. C., SHORR, E., AND HARTMAN, C. G.: A comparative study of the vaginal smear cycle of the Rhesus monkey and the human. *Carnegie Inst. Wash. Publication* 557, Contributions to Embryology, 31: 1, 1943.
- C. Influence of ovarian and gonadotrophic hormones; clinical applications:*
6. PAPANICALAOU, G. N., AND SHORR, E.: The action of ovarian follicular hormone in the menopause, as indicated by vaginal smears. *Am. J. Obst. & Gynec.*, 31: 806, 1936.
7. SHORR, E.: Effect of concomitant administration of estrogens and progesterone on vaginal smear in man. *Proc. Soc. Exper. Biol. & Med.*, 43: 501, 1940.
8. SHORR, E., AND PAPANICALAOU, G. N.: Action of gonadotropic hormones in amenorrhea as evaluated by vaginal smears. *Proc. Soc. Exper. Biol. & Med.*, 41: 629, 1939.
9. SHORR, E., PAPANICALAOU, G. N., AND STIMMEL, B. F.: Neutralization of ovarian follicular hormone in women by simultaneous administration of male sex hormone. *Proc. Soc. Exper. Biol. & Med.*, 38: 759, 1938.
10. PAPANICALAOU, G. N., RIPLEY, H. S., AND SHORR, E.: Inhibitory effects of male sex hormones on human menstruation and their evaluation by vaginal smears. *Proc. Soc. Exper. Biol. & Med.*, 37: 689, 1938.
11. SHORR, E.: The menopause. *New York Acad. of Med. Bull.*, 16: 453, 1940.
12. CAMPBELL, R. E., AND SEVRINGHAUS, E. L.: Pituitary gonadotrophic extracts for treatment of amenorrheas, menorrhagia and sterility. *Am. J. Obst. & Gynec.*, 37: 913, 1939.
13. SHORR, E., ROBINSON, F. H., AND PAPANICALAOU, G. N.: A clinical study of the synthetic estrogen stilbesterol. *J. A. M. A.*, 113: 2312, 1939.
14. RUBENSTEIN, B. B.: The vaginal smear—basal body temperature technic and its application to the study of functional sterility in women. *Endocrinology*, 27: 843, 1940.
- D. The vaginal smear in cancer of the genital tract:*
15. PAPANICALAOU, G. N., AND TRAUT, H. F.: Diagnosis of uterine cancer by the vaginal smear. *The Commonwealth Fund*, 1943.
16. MEIGS, J. V., GRAHAM, R. M., FREMONT-SMITH, M., KAPNICK, I., AND RAWSON, R. W.: The value of the vaginal smear in the diagnosis of uterine cancer. *Surg., Gynec. & Obst.*, 77: 449, 1943.

## MOENCKEBERG'S SCLEROSIS

### A CLINICAL ENTITY

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The clinical characteristics which distinguish Moenckeberg's Sclerosis from other forms of arteriosclerosis are extreme calcification of the arteries of the lower extremities in young or middle-aged people who have no symptoms or signs of impaired circulation. The calcification of the blood vessels is usually discovered by accident when an x-ray is made for arthritis, fracture or some other bone or joint condition. Physician and patient are frequently so surprised and disconcerted by the unusual findings that treatment of the condition for which the x-ray was made is neglected, and measures are immediately instituted to improve circulation in the legs. In the general panic, the fact that the circulation is entirely normal is completely disregarded. Actually the prognosis of Moenckeberg's Sclerosis, as pointed out by Moschcowitz (1), is favorable. Patients who have been observed for years have shown no tendency to develop impaired circulation or other serious sequelae.

Pathologically, Moenckeberg's Sclerosis is characterized by a deposit of calcium in the media of the arteries. There is no thickening of the intimal layer, which is the most striking feature in true arteriosclerosis, and the blood vessel lumen is therefore not narrowed. The surface of the intima remains uninjured and thrombosis does not occur.

Roentgenologically, the most typical cases show calcification of the leg arteries in the form of a chain of rings, like a goose neck. The calcification may extend upward beyond the pelvic brim and may be found in the brachial artery.

The clinical features are the complete absence of any symptoms or signs of impaired circulation in the extremities. All pulsations are easily felt and are normal in size. Oscillometric and temperature studies indicate a normal blood flow. No thickening of the blood vessels is noted on palpation. Up to the present time all cases of Moenckeberg's Sclerosis that we have seen have been in the male sex. The clinical course is benign, and no case followed has developed thrombosis.

The disease is infrequent. Only 13 instances of Moenckeberg's Sclerosis have been observed in approximately 2600 cases of arteriosclerotic peripheral vascular disease seen by the senior author in his private practice, making an incidence of 1 case in 200.

The following histories reveal the clinical features of the disease:

*Case 1. History:* M. A., aged 27 years, physician, was seen in August, 1937. Two months previously the patient had developed an ulcer at the inner side of the right ankle, following a poison ivy rash which involved the whole right leg. X-ray examinations of the legs had shown extensive and marked calcification of the blood vessels. The patient had no other complaints. His urine had been negative for sugar on several occasions.



*Examination:* There was a complete situs inversus of the chest organs and the gastrointestinal tract. All extremity pulses were patent in both upper and lower limbs. The arteries were soft on palpation. Oscillometric readings were normal at both ankles. The only abnormal finding was a punched out ulcer, 1½ inches above the right internal malleolus. The x-ray examination of both legs revealed extensive and marked calcification of all thigh and leg arteries.

*Course:* The ulcer subsequently healed with cod liver oil ointment and supportive bandaging. In 1944 this patient was in good health and had had no trouble with his legs.

*Case 2. History:* L. K., aged 33 years, dentist, was seen in September, 1943. He had been an army officer for some time. A few weeks prior to the examination he noticed some weakness in the left leg while standing. The rest of his history was non-contributory. He smoked about four cigarettes a day. He was studied in one of the Army hospitals. When x-ray examinations of the lower extremities were taken, calcification of the blood vessels was found. Blood examination on several occasions had revealed: Sugar 100 mg. per 100 cc., uric acid 4.4, 4.1, 4.3 mg. per 100 cc., calcium 10, 10.5 mg. per 100 cc. and cholesterol 304, 224 mg. per 100 cc. The basal metabolism was normal.

*Examination:* All foot and wrist arteries were normally patent. Oscillometric readings were 5 at both ankles. The findings pertaining to his joints and to his central and peripheral nervous system were negative. X-ray examination revealed extensive calcification of the lower extremity arteries.

*Case 3. History:* A. A. W., aged 34 years, attorney, was seen in September, 1938. Two years previously the patient developed continuous pain in his right foot. He was x-rayed and calcification of the blood vessels was noted. On this account, he was treated by a specialist for vascular diseases with intravenous saline injections, hot baths and postural exercises. At the time of the examination, his complaints were a continuous pain in his right foot, pains in the arms and in the back of his head. He never had had intermittent claudication. He had given up smoking at the time the calcification in his blood vessels was discovered. It may be of interest that electrocardiograms taken prior to the examination were normal. The rest of his history is irrelevant.

*Examination:* The patient was an obese apprehensive young man. He exhibited an emotional tachycardia and showed some thickening of the radial arteries. Both dorsalis pedis arteries were absent (normal variation). All the other foot pulses were normal. Oscillometric readings showed 4.5 at both ankles. X-ray examinations of the legs revealed marked calcification of almost all thigh, leg and foot arteries.

*Case 4. History:* H. G., aged 41 years, was seen in April, 1943. For six months prior to the examination he had had pains in the left thigh, sometimes after walking, occasionally at rest. An x-ray examination had revealed calcification of the femoral arteries. The patient's right eye had been almost blind since 1939, when he suffered a detachment of the retina due to an exudative choroiditis following osteomyelitis of the upper jaw. The patient smoked fifteen cigarettes a day. He had no other complaints.

*Examination:* The patient was a well nourished, middle-aged man. His right eye showed a dense cataract and was blind. Blood pressure was 125 systolic and 82 diastolic. All extremity arteries were normally patent. Oscillometric readings were 4.5 at both ankles.

X-rays examinations revealed extensive calcification of both femoral arteries as well as the posterior tibial and peroneal arteries.

*Laboratory Data:* The urine contained a trace of albumin but was otherwise normal. Blood studies revealed cholesterol 199 mg. per 100 cc., sugar 153.8 mg. per 100 cc., calcium 9.0 mg. per 100 cc., phosphorus 2.5 mg. per 100 cc. (Dr. Nathan Rosenthal). In view of the high fasting blood sugar level, a glucose tolerance curve was obtained and showed 133.2 fasting—186.0 (30 minutes)—151.4 (60 minutes). It was interpreted as normal with slightly elevated figures by Dr. Rosenthal. Blood Kahn reaction was negative.

*Case 5. History:* M. B., aged 44 years, physician, was seen in December, 1943. Several months prior to the examination, he tore the semilunar cartilage of his left knee in an accident. For many years previously he had suffered from arthritis of the left knee. The

patient came for an examination because x-rays taken on the occasion of the accident had shown calcification of the lower leg arteries bilaterally.

The patient was a heavy smoker. He complained of precordial discomfort after smoking. However, repeated electrocardiographic examinations had been normal (Dr. Boas) and he had been found to be sensitive to tobacco in allergy tests done by Dr. Harkavy. He had passed a kidney stone, supposedly composed of uric acid, several years prior to examination. The rest of his medical history was irrelevant. He had never had intermittent claudication.

*Examination:* The patient was a young-looking, well nourished, middle-aged man. The physical findings were normal throughout. All ankle and wrist pulses were present and soft. Oscillometric readings were 4 at the right ankle and 4.5 at the left ankle.

X-ray examination of the legs showed marked calcification of both posterior tibial arteries, more pronounced on the left side, and some calcification of the dorsalis pedis arteries.

*Case 6. History:* W. E. F., aged 44 years, storekeeper, was seen in April, 1942. For 7 years prior to the examination, he had had pain and swelling in both ankles which had been treated successively with arch supports, bed rest, hot and cold applications, intermittent venous occlusion and massage, with only fair results. His ankle pains were worse in the morning and improved somewhat after walking. He had had an occasional pain in the left shoulder. An ingrown right great toe nail had been removed a few years previously. The rest of his history was irrelevant.

*Examination:* The patient was a well nourished middle-aged man. Except for a palpable spleen, there were no abnormal findings. Blood pressure was 105 systolic and 75 diastolic. All upper and lower extremity pulsations were normal. The vessels were soft on palpation. Oscillometric readings were 3.5 at the right and 4 at the left ankle. Both ankles were enlarged, warm and tender. The feet were moderately inverted and the arches were flattened. There was some limitation of motion of the right ankle joint. The urine was normal.

X-ray examination of the legs showed extensive calcification of both femoral and posterior tibial arteries.

*Case 7. History:* B. S., aged 44 years, executive, was seen in July, 1939. For many years he had been complaining of heaviness in his legs and occasionally of cramps in the calves at night. More recently he had had an inconstant pain on the right heel on walking and throbbing in his feet on standing. X-rays of his legs had shown calcification of the blood vessels. Except for removal of the cecum and appendix 25 years previously his history was non-contributory.

*Examination:* The patient was an overweight, gray-haired, middle-aged, very apprehensive and emotional man. The general physical examination was negative. Blood pressure was 110 systolic and 80 diastolic. Except for a healed right lower rectus scar, the abdomen was negative. All pulsations in both upper and lower extremities were easily felt. The right posterior tibial artery appeared to be slightly narrower than the left on several occasions. Oscillometric readings were 5 at both ankles. There was a moderate flattening of the foot arches. The urine showed traces of albumin, was otherwise normal. Laboratory examinations by Dr. Nathan Rosenthal showed hemoglobin, 112 per cent; red blood cells, 5,580,000; white blood cells, 7,550; platelets 270,000; cell volume 47.9 per cent; and plasma volume 52.1 per cent. The blood picture was regarded as normal. X-ray examination of his legs always showed marked and extensive calcification of the arteries, both of the thighs and the legs.

*Case 8. History:* J. M., aged 45 years, merchant, was seen in November, 1942. For 10 years he had suffered from lower back pain. Two years previously he developed a right-sided sciatica which recurred one year later. For three months he had cramps at night in his right calf, and occasionally painful twitching in the calf muscles lasting from a few seconds to a few minutes. X-ray examination had shown calcification of the blood vessels. He had been treated with depromanex, short wave, erythroltetranitrate, liquor and phenobarbital. However, the night cramps had not improved. The rest of the history was non-contributory.

*Examination:* A well nourished middle-aged man, whose physical status was entirely negative. Blood pressure was 115 systolic and 70 diastolic. All pulses were patent in both upper and lower extremities. Oscillometric readings were 4 at the right and 4.5 at the left ankle. There was some weakness of the foot arches. Urine examination was normal. X-ray examination disclosed extensive calcification in all lower extremity arteries up to the level of the lesser trochanter. The upper extremity vessels were not calcified. The blood count was normal. Uric acid in the blood was 4.4 and 5.0 mg. per 100 cc., cholesterol 264 and 162 mg. per 100 cc., calcium 12 mg. per 100 cc. and phosphorus 3.4 mg. per 100 cc.

*Case 9. History:* D. C., aged 46 years, was seen in March, 1944. For 10 years he had had lumbago every year. Two and one half years previously he had developed a sciatica in his left leg. Despite various forms of treatment (traction, belt, brace, injections, massage, baking, chiropractic handling, x-rays) he continued to complain of numbness in the left great toe and persistent drawing sensation in the left calf. He had never had intermittent claudication. The rest of his history was irrelevant.



FIG. 1. Calcification of the pelvic arteries (Case 10).

*Examination:* The patient was a well nourished middle-aged man. Physical status was negative. Blood pressure was 115 systolic and 80 diastolic. All extremity arteries were open and soft. Oscillometric readings showed 4 at the right ankle, 3.5 at the left ankle. There was hypesthesia of the left leg. The reflexes were normal and equal. Both foot arches were somewhat flattened. Urine was normal.

X-ray examination of both legs showed marked calcification in the blood vessels, particularly around the left ankle.

*Case 10. History:* M. R., aged 46 years, printer, was seen in April, 1943. For 4 months he complained of pain in his right knee which increased when he started to walk after he had been sitting. He had no other complaints. He smoked an occasional cigarette. X-ray examination of his knees had been taken which showed no joint pathology but marked calcification of the popliteal arteries.

*Examination:* The patient was an obese, middle-aged, slightly gray-haired man. Physical status was negative. Blood pressure was 115 systolic and 80 diastolic. All extremity pulsations were easily felt. Oscillometric readings were 5 at both ankles. There were some varicose veins in the popliteal fossa. The right knee was somewhat warm and swollen, and had a point of tenderness over the inner condyle of the femur. X-ray examination showed

marked calcification of the pelvic (figure 1) and lower extremity vessels throughout. His right brachial artery also was calcified (figure 2). Blood cholesterol was 113 mg. per 100 cc., calcium 9 mg. per 100 cc., phosphorus 7.8 mg. per 100 cc. (Dr. N. Rosenthal). There were traces of albumin in the urine which otherwise was normal.

*Case 11. History:* A. S., aged 47 years, was seen in June, 1938. For 20 years he had pains in both feet, more on the left side during the day and night. He was treated for varicose veins and had also been given intravenous injections and other medicines by mouth without much benefit. He had no other complaints. He had never smoked.



FIG. 2. Calcification of the brachial artery (Case 10).

*Examination:* The patient was a gray-haired man who showed normal physical findings. All pulses in the four extremities were present and normal. There were large recurrent varicose veins with a positive Trendelenburg sign on both sides. Longitudinal healed scars could be seen along both legs. The foot arches were flattened. Oscillometric readings were 5 at both ankles. X-ray examination of the legs revealed extensive and marked calcification of the arteries.

*Case 12. History:* W. M. H., aged 51 years, insurance agent, was seen in November, 1941. For a few months he had complained of pain in both legs on standing which was relieved by

walking. He thought his left calf was somewhat swollen. For 5 years he had complained of a sticking pain in his left arm on moderate exertion. This condition was diagnosed and treated by a heart specialist as coronary artery disease. There were slight electrocardiographic changes. The patient did not smoke. The rest of his history was non-contributory.

*Examination:* The patient was a tall, well nourished, middle-aged man. All extremity pulses were normally patent. Oscillometric readings showed 5 at the right ankle and 4.5 at the left ankle. There were bilateral varicose veins and some flattening of the foot arches.



FIG. 3. Calcification of the popliteal artery (Case 12).

The urine showed a trace of albumin and was otherwise normal. X-ray examination disclosed marked calcification of popliteal and lower leg arteries (figure 3).

*Case 13. History:* M. I. C., aged 52 years, furrier, was seen in July, 1944. For the past 3 years, he had complained of constant pain in his right hip, day and night. The pain increased on standing, and was relieved on walking. For several weeks he had had cramps in both calves at night. He had a radical operation for varicose veins 27 years ago. The disease recurred 4 years post-operatively. The patient never had intermittent claudication. He had never smoked.

*Examination:* Patient was an obese man. Physical status was negative. Blood pressure was 140 systolic and 80 diastolic. There were extensive varicose veins bilaterally with



a positive Trendelenburg sign. Healed longitudinal scars were noted along both legs. All extremity arteries were normally patent. Oscillometric readings showed 4 at both ankles. Urine examination and blood count were normal.

X-ray examination disclosed extensive calcification in the blood vessels of both lower extremities (figure 4).

*Case 14. History:* A. L., aged 54 years, mechanic, was seen in March, 1943. He complained of pains in his right great toe, pains in the knees, pain and stiffness in the fingers particularly in the morning. He had been treated for arthritis for 7 years. He also had



FIG. 4. Calcification of the posterior tibial artery (Case 13).

suffered for many years with chest pain, radiating to the back. This increased on moderate effort, and he could not walk more than three blocks without stopping. He smoked 2 cigars a day. The rest of his history was irrelevant.

*Examination:* The patient was a gray-haired, undernourished, middle-aged man. He had a marked arcus senilis. Physical examination was otherwise negative. Blood pressure was 145 systolic and 95 diastolic. All extremity pulses were normally patent. The oscillometric readings were 5 at both ankles. The foot arches were flattened. The urine showed a trace of albumin, and was otherwise normal. X-rays of the lower extremities disclosed slight arthritic changes in both knees, and extremely advanced calcification in the leg arteries.

## DISCUSSION OF THE CLINICAL MANIFESTATIONS

The common features in the 14 cases reported were the absence of a history of intermittent claudication or any other symptoms suggestive of peripheral arterial disease; the presence of normally patent arteries in all four extremities and of normal oscillometric readings; the presence of marked and extensive calcification of the blood vessels in the lower extremities. The blood pressure in the entire group was normal. In no case has a thrombosis of an artery occurred during the period of observation.

Two of the older patients (cases 12 and 14) showed symptoms and signs indicating arteriosclerosis of the coronary arteries. No evidence of the usual intimal type of arteriosclerosis was present in the other 12 cases. Typical uncomplicated Moenckeberg's Sclerosis is seen between the ages of 25 and 40. In this group of 14 cases, the ages ranged from 27 to 54 years. With advancing age, patients with Moenckeberg's Sclerosis may be expected to develop intimal arteriosclerosis in the same way as other individuals. It is not surprising, therefore, that in the older patients of our group evidence of intimal arteriosclerosis was found. The occurrence of both diseases in one individual appears to be due to coincidence; it does not indicate that both processes have the same etiology or pathogenesis. The association of both diseases in the same patient masks the distinctive features of Moenckeberg's Sclerosis. It is perhaps for this reason that the clinical literature concerning this disease is so confused.

Three of our patients complained of cramps in the calf muscles which occurred at night and awakened them from sleep. The cause of such cramps is not clearly understood. However, they are usually promptly relieved by oral administration of calcium lactate in small doses. This suggests that there may be some disturbance in calcium metabolism in these patients. The characteristic primary calcification of the blood vessels appears to point in a similar direction.

In most cases calcification was not noted above the pelvic brim. In case 10 the calcification was more extensive, involving the pelvic arteries and also the left brachial artery.

## REVIEW OF LITERATURE

There is considerable debate at the present time as to the true nature of arteriosclerosis. For the past 100 years there have been two schools of thought. One group maintains that arteriosclerosis is a primary degenerative disease of the intima of the large, medium and small arteries, which is associated with thickening due to hyperplasia, hyalinization and deposition of fatty and other materials (2). The other group regards arteriosclerosis simply as a primary deposition of fatty material from the blood stream into the arterial wall (3). Both groups agree that the sequence of events is as follows: Lipoid and other material appear in the intima and media of these arteries, often followed by calcification. Thickening of the intima usually occurs, causing narrowing of the vessel lumen which leads to interference with normal circulation in various organs. Subsequently, the media and adventitia of the diseased vessel may

thicken due to the deposition of fatty, calcified and other material and to proliferation.

It occurred to Virchow in 1856 that, from the morphological point of view, a distinction should be drawn between intimal arteriosclerosis and media "petrification" (4). It was Moenckeberg who first ventured the opinion that these two processes have a different pathogenesis and perhaps a different etiology (5).

Histologically, Moenckeberg's Sclerosis develops in three stages (6). First, fine granules of calcium salts are found near the internal elastic membrane (7) and in the connective tissue between the muscle fibers in the media, often in the centre of the media. In this stage, the media muscle fiber nuclei may be clearly stainable. This indicates that the primary change is not a degeneration

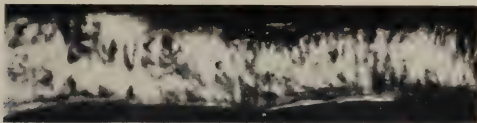


FIG. 5. Medial calcification of femoral artery.



FIG. 6. Medial calcification of femoral artery. Note retraction of the intima over the area of calcification.

of the muscular layer of the media (8), as had been maintained by older authors (9). In the second stage, the lime salt granules extend in the media, coalesce and soon form plates and welded rings surrounding the whole lumen of the artery (figures 5 and 6). The muscle fibers degenerate, but their nuclei are stainable for a comparatively long time. The disappearance of the muscle fibers at this stage was thought to be due to atrophy caused by pressure (10). In the third stage, a reparative inflammation sets in around the foci of calcification, comparable to a foreign body reaction, and the adventitia shows changes in the form of hyaline degeneration of the connective tissue and thickening of the vasa vasorum (6). In later stages, bone may form at the site of former calcifications, with Haver's canals (11). Fractures, with fibrous union, of such arteries have been reported (12).

Several authors have discussed the relationship of Moenckeberg's Sclerosis to arteriosclerosis. The discussion has been led by pathologists, and a wealth of anatomical, histological and statistical material has been brought forward. In pathological material Moenckeberg's Sclerosis is often encountered in individuals affected by generalized arteriosclerosis, which may account for the fact that many pathologists regard both as one disease (13). Others, though aware of the different anatomical appearance, leave the question of identity open (14). Only a few pathologists hold that they are two pathogenetically and etiologically different processes (15).

Little has been presented in the literature describing the clinical picture of Moenckeberg's Sclerosis. Autopsy reports of typical cases are lacking. Because of the benign course of the disease, opportunities for post mortem studies in the early stages seldom occur. Unfortunately, experimental work on arteriosclerosis has not helped in clarifying the nature of Moenckeberg's Sclerosis.

#### EXPERIMENTAL WORK

Intimal changes have been produced in herbivora and in fowl by feeding with cholesterol and by other experimental methods (16). They resemble human arteriosclerosis, but differ in some important points (17).

A picture similar to Moenckeberg's Sclerosis can be produced by different agents. Adrenalin and large doses of vitamin D produce changes most closely resembling human media calcification (18). Variations in experimental technic, however, may produce primary intimal changes as well (19). B. Fischer observed adrenalin media necrosis and calcification associated with intimal sclerosis in the same aorta of the rabbit, when he cut the depressor nerve. Moenckeberg (20) maintained that experimental media calcification differs from human media sclerosis. Experimental calcification is the end result of an inflammatory reaction around foci of necrosis within the media musculature, caused by the various agents. Intimal thickening is often associated with it. Moenckeberg's Sclerosis, however, is thought to be a primary dystrophic process of the media ground substance (6); histologically, no inflammatory changes preceding the deposition of lime salt granules have been found (10). These degenerative changes reminded Moenckeberg of dystrophic calcifications in other organs and tissues.

Thus, experimental studies have not contributed to the understanding of human media calcification.

#### OBSERVATIONS IN MAN

*Autopsy reports.* Among 130 autopsies, Moenckeberg found media calcification, not associated with intimal sclerosis, in 33 per cent. In view of the rarity of the disease in our experience, we hesitate to accept this figure as representative. In Moenckeberg's cases, the process was located more often in the femorals than the radials. The aorta was rarely involved.

In contrast to the frequent involvement of the coronary arteries by intimal arteriosclerosis, media calcification does not involve these arteries (10). Generally, the frequency distribution in single vessels is distinctly different for media

calcification as compared with arteriosclerosis, since most cases of media calcification involve the pelvic and extremity arteries, whereas intimal arteriosclerosis is most frequently located in the aorta, cerebral, renal and coronary arteries.

It has been repeatedly reported that the arteries near the great joints are not involved with media calcification. Moenckeberg confirmed this observation (21). However, in our series a few cases show involvement of the popliteal and brachial arteries (figures 2 and 3).

*Clinical observations.* Moenckeberg's Sclerosis is often mentioned in the clinical literature, but it is difficult to gain a clear picture of the disease from these reports. Many clinicians seem to think Moenckeberg's Sclerosis is a senile degenerative disease (22); others state it occurs mostly in conditions of marasmus or cachexia (23); some do not want to have it differentiated from intimal arteriosclerosis (24); and a few leave the question of identity open (25).

#### COMMENTS

The impression gained from a review of the entire clinical and pathological literature is that there is utter confusion concerning Moenckeberg's Sclerosis. Perhaps this is due to the fact that the disease runs a benign course. There is rarely an opportunity to study the pathological changes in early cases when the picture is not confused by superimposed arteriosclerosis. Furthermore, typical instances of Moenckeberg's Sclerosis are relatively rare and since they present no serious complaints they are seldom admitted to hospitals, where critical study of the problem could be made. In fact, most cases are discovered by accident when x-rays are made to investigate some other condition. We believe that the clinical picture of Moenckeberg's Sclerosis is distinctive and there should be no confusion.

*Diagnosis.* The disease occurs in young and middle-aged males who present no symptoms or signs of impaired circulation in the extremities or elsewhere. X-rays of the lower extremities reveal extensive calcification of the blood vessels, occasionally extending into the pelvic arteries and sometimes calcification in the vessels of the upper extremities. Clinical evidence of arteriosclerosis of the cerebral, coronary, renal arteries and the aorta is absent. No consistent chemical and morphological changes in the blood are found. In a number of our cases a striking symptom has been the occurrence of cramps in the calf muscles during sleep. Such cramps were readily relieved by calcium lactate in small oral doses. This fact together with the pathological reports of primary deposition of calcium salts in the media of the arteries suggests some disturbance of calcium metabolism in patients with Moenckeberg's Sclerosis. However, further investigation will be necessary to determine if this is true. The disease characteristically runs a benign course and there appears to be no tendency to major arterial thrombosis. The prognosis is good and no treatment of any kind appears to be indicated.

#### SUMMARY

1. The clinical history of 14 cases of Moenckeberg's Sclerosis has been presented.



2. Review of the pathological, clinical and experimental literature has been made.
3. The distinctive clinical picture of Moenckeberg's Sclerosis has been defined.

## REFERENCES

1. MOSCHCOWITZ, E.: Vascular Sclerosis. New York, Oxford University Press, 1942, p. 76.
2. ASCHOFF, L.: In Cowdry's Arteriosclerosis. New York, The MacMillan Co., 1933, p. 3.
3. HIRSCH, E. F., AND WEINHOUSE, S.: The role of the lipids in Atherosclerosis. *Physiol. Rev.*, 23: 185, 1943.
4. VIRCHOW, R., CIT. MOENCKEBERG, J. G.: Mediaverkalkung und Atherosklerose, *Virchows Arch. f. path. Anat.* 216: 408, 1914.
5. MOENCKEBERG, J. G.: Ueber die reine Mediaverkalkung der Extremitaetenarterien und ihr Verhalten zur Arteriosklerose, *Virchows Arch. f. path. Anat.* 171: 141, 1903.
6. JORES, L.: Arterien, in Henke and Lubarsch, *Handb. d. spez. pathol. Anat. u. Histol.*, Berlin, 2: 632, 1924.
7. HUECK, W.: Anatomisches zur Frage nach Wesen und Ursache der Arteriosklerose. *München. Med. Wehnschr.* 19: 535, 1920.
8. HUECK, W.: Ueber das Mesenchym, *Beitr. z. pathol. Anatomie*, 66: 330, 1920.
9. BENDA, C.: Die Arteriosklerose im Lichte d. experimentellen Forschung, *Ther. Gegenw.*, 1909, p. 121.
10. FABER: Die Arteriosklerose, Jena, 1912, p. 81.
11. MOENCKEBERG, J. G.: Ueber Knochenbildung in der Arterienwand, *Virchows Arch. f. path. Anat.* 167: 191, 1902.
12. KLOTZ, O.: Fractures of arteries. *J. Med. Res.*, 34: 495, 1916.
13. MARCHAND, F.: Ueber Arteriosklerose, *Ref. Verh. d. 21. Kongr. inn. Med.* p. 23, 1904.
14. MCCALLUM, C.: Textbook of Pathology, Philadelphia and London, W. B. Saunders Co., 1917, p. 331.
15. BOYD, W.: The Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1932, p. 119. JORES, L., see 6.
16. ANITSCHKOW, N.: Experimental Arteriosclerosis in Animals, in Cowdry's Arteriosclerosis, see 2, p. 271.
17. DUFF, G. L.: Experimental cholesterol arteriosclerosis and its relationship to human arteriosclerosis. *Arch. Path.*, 20: 81, 259, 1935.  
———The nature of experimental cholesterol arteriosclerosis in the rabbit. *Arch. Path.*, 22: 161, 1936.
18. ERB, W.: Experimentelle und Histologische Studien ueber Arterienerkrankungen nach Adrenalininjektionen, *Arch. f. exper. Pathol. u. Pharmak.* 53, 1905.  
FISCHER, B.: Zur Frage der experimentellen Arteriosklerose durch Adrenalininjektionen, *Klin. Wehnschr.*, 1907.  
SCHIFF, A.: Die durch Vigantol erzeugbaren Gefaessveraenderungen und ihre Rueckbildungsaefahigkeit im Tierversuch, *Virchows Arch. f. path. Anat.* 278: 62, 1930.
19. FISCHER, W., AND JAFFE, B.: Arteriosklerose, in *Handb. d. norm. u. pathol. Physiologie (Bethe-Bergman)* 7-2: 1088, 1927.
20. MOENCKEBERG, J. G.: *Zblt. f. allg. Pathol. u. Pathol. Anat.* 34: 612, 1924.
21. OBERNDORFER: Beitrag z. Frage d. Lokalisation arteriosklerotischer Prozesse i.d. peripheren Arterien, *Dtsch. Arch. klin. Med.* 21: 515, 1911.  
MOENCKEBERG, J. G.: Arterienverkalkung, in *Therapie d. Herzinsuffizienz*, Thieme, 1924, p. 63.
22. PIERSON, M. S.: Recent advances in therapy of arteriosclerosis. *Bull. New York Acad. Med.* 18: 36, 1942.
23. Savill's System of Clinical Medicine, London, E. Arnold & Co., 1939, p. 138.
24. ROMBERG, E.: *Lehrb. d. Krankheiten d. Herzens u.d. Gefaesse*, Enke, 1925, p. 641.
25. ALLBUTT, SIR CLIFFORD: Disease of the Arteries, London, McMillan & Co., 1915, p. 482.

## THE BLOOD IODINE IN THE PERIOD AFTER THYROIDECTOMY<sup>1</sup>

SOLOMON SILVER, MAJOR, M.C., A.U.S., with the technical assistance of  
MARY CATHERINE TYSON, M.D.

It is a great privilege for me at this time to make a small contribution to the volume of the Journal of The Mount Sinai Hospital honoring my friend and chief, Dr. Eli Moschcowitz. It is a particular pleasure to put these facts and thoughts together while I am many thousand miles away from home and my friends at the hospital, looking forward to the day when we shall all return to civilian life and resume our hospital activities.

In earlier studies (1) dealing with iodine metabolism the following facts were established:

1. All the normally circulating blood iodine can be extracted with ethyl alcohol if proper precautions are taken. The distinction between "organic" and "inorganic" blood iodine based on alcohol solubility is without foundation, and significant quantities of "inorganic" iodine in normal blood exist only as an artifact of chemical manipulations.

2. Practically all the normally circulating blood iodine is in the plasma. The amount present in washed blood cells is too low to be determined by present methods.

3. All the normally circulating blood iodine and that circulating in Graves' disease is in the plasma in a form which resists dialysis and is probably bound to protein.

4. Dialysis removes from the blood or plasma all iodine added or ingested in the form of iodide and can be used to remove ingested iodide known to the observer or unsuspected by him.

5. Dialysis does not completely remove from the plasma added or ingested iodine in the form of di-iodotyrosine or thyroxine or some other organically bound iodine compounds.

On the basis of these observations a series of patients suffering from Graves' disease was studied before and after medical and surgical treatment and serial determinations of the protein-bound, plasma iodine were made in an attempt to study the correlation between the level of the plasma iodine and the clinical phenomena of Graves' disease, particularly in the postoperative period. So far as we know such studies have never appeared in the literature except for isolated single case reports employing methods now known to be inadequate.

*Procedure:* Only patients with obvious Graves' disease were used in this study and only those upon whom surgical therapy was practiced will be reported here. Upon admission to the medical service a period of stabilization lasting several days was carried out. During this period several determinations of the basal metabolic rate were performed and the first determination of the blood

<sup>1</sup> This paper is based on studies carried out while the author was attached to the medical service and laboratories of The Mount Sinai Hospital, New York City, during 1941-1942.

iodine was done. Iodine was then administered in the form of U.S.P. Lugol's Solution, ten minims three times a day, until maximum chemical improvement was obtained, usually about 18 days. On the day before the scheduled operation the basal metabolic rate was again determined and then a second determination of the plasma iodine was made immediately upon the return of the patient from the operating room and again 24 and 72 hours after operation. Only those patients for whom fairly complete data was available are included in this report.

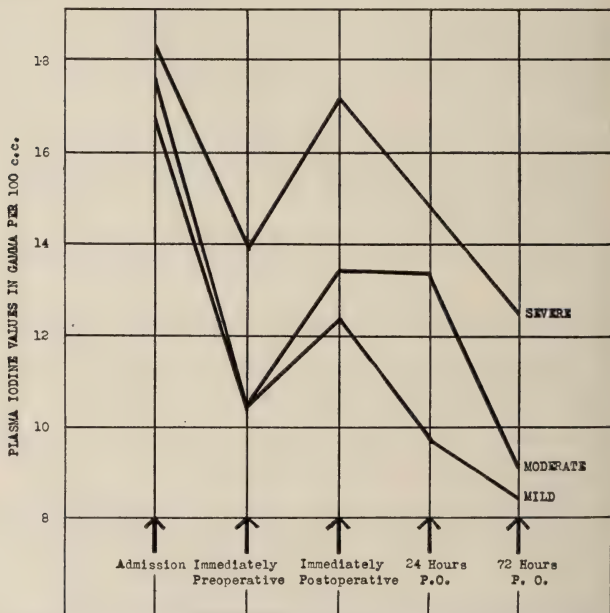


FIG. I. Chart showing average plasma iodine levels before and after operation in the groups of cases characterized clinically by mild, moderate and severe postoperative reactions

An independent study was made of the clinical course of each patient without reference to the chemical findings. These cases were then classified as to the severity of their postoperative reaction into groups designated as mild, moderate, and severe. This classification took into account the febrile response, the pulse rate, the psychic reaction and a general clinical estimate of the entire status of the patient. As noted, this clinical evaluation of postoperative reaction was done by one of us (C. T.) without any knowledge of the results reached in the chemical

TABLE 1

| CASE NUMBER                      | SEX | AGE | DURATION OF DISEASE IN YEARS | B. M. R. ON ADMISSION | RECENT IODINE MEDICATION | NUMBER OF DAYS ON LUGOL'S SOLUTION | B. M. R. PREOPERATIVE | TYPE OF OPERATION | PLASMA IODINE ON ADMISSION | PLASMA IODINE AFTER LUGOL'S SOLUTION (PRE-OPERATIVE) | PLASMA IODINE IMMEDIATELY POST-OPERATIVE | PLASMA IODINE 24 HOURS POST-OPERATIVE | PLASMA IODINE 72 HOURS POST-OPERATIVE | REMARKS   |
|----------------------------------|-----|-----|------------------------------|-----------------------|--------------------------|------------------------------------|-----------------------|-------------------|----------------------------|--|--|---------------------------------------|---------------------------------------|---|
| Mild postoperative reactions     |     |     |                              |                       |                          |                                    |                       |                   |                            |  |  |                                       |                                       |   |
| 1                                | F   | 43  | 10                           | 45                    | Yes                      | 30                                 | 22                    | Hemi              | 13.8                       | —  | 12.3                                     | 9.0                                   | 8.6                                   | First stage<br>Case 17                            |
| 2                                | M   | 42  | 6                            | 34                    | Yes                      | 14                                 | 20                    | Hemi              | —                          | 12.6   | —  | 10.3                                  | 8.1                                   |   |
| 3                                | M   | 58  | 8                            | 41                    | Yes                      | 10                                 | 20                    | Hemi              | 10.0                       | 6.3  | 7.0                                      | 6.2                                   | —                                     |   |
| 4                                | F   | 63  | 2                            | 51                    | No                       | 19                                 | 16                    | Sub-total         | 14.5                       | 10.5   | 13.2                                     | 10.5                                  | 8.1                                   |   |
| 5                                | F   | 33  | $\frac{1}{2}$                | 73                    | No                       | 21                                 | 25                    | Sub-total         | 20.6                       | 11.8   | 14.4                                     | 10.6                                  | 8.5                                   |   |
| 6                                | F   | 51  | 1                            | 70                    | No                       | 18                                 | 34                    | Sub-total         | 20.2                       | 8.8  | 13.3                                     | 10.1                                  | 8.7                                   |   |
| 7                                | F   | 52  | 1                            | 54                    | No                       | 13                                 | 24                    | Sub-total         | 23.1                       | 16.0   | 18.2                                     | 13.1                                  | 11.2                                  |   |
| 8                                | F   | 34  | 2                            | 7                     | ?                        | 11                                 | 6                     | Sub-total         | 16.7                       | 7.5  | 6.8                                      | 11.3                                  | 5.5                                   |   |
| 9                                | F   | 57  | 2                            | 89                    | No                       | 19                                 | 29                    | Sub-total         | 20.2                       | 9.9  | 14.0                                     | 8.0                                   | 8.3                                   |   |
| 10                               | F   | 40  | $\frac{1}{3}$                | 40                    | Yes                      | 16                                 | 31                    | Hemi              | 17.1                       | 11.8   | —  | 8.4                                   | 6.8                                   |   |
| Average .....                    |     |     |                              |                       |                          |                                    |                       |                   | 17.4                       | 10.6   | 12.4                                     | 9.8                                   | 8.2                                   |   |
| Moderate postoperative reactions |     |     |                              |                       |                          |                                    |                       |                   |                            |  |  |                                       |                                       |   |
| 11                               | F   | 52  | $\frac{1}{2}$                | 34                    | No                       | 32                                 | 29                    | Hemi              | —                          | 12.4   | 17.3                                     | 18.0                                  | 12.6                                  |   |
| 12                               | F   | 57  | 3                            | 60                    | No                       | 40                                 | 31                    | Sub-total         | 13.3                       | 10.4   | 15.7                                     | 7.1                                   | 6.8                                   |   |
| 13                               | F   | 30  | $\frac{1}{2}$                | 60                    | No                       | 17                                 | 22                    | Sub-total         | 22.0                       | 11.3   | 10.9                                     | 9.3                                   | 7.8                                   |   |
| 14                               | F   | 63  | 1                            | 55                    | No                       | 20                                 | 12                    | Sub-total         | 17.0                       | 9.4  | 9.5                                      | 6.7                                   | 5.9                                   |   |
| 15                               | F   | 31  | 2                            | 68                    | No                       | 15                                 | 32                    | Sub-total         | 20.5                       | 7.4  | 10.3                                     | 10.8                                  | 7.8                                   |   |
| Average .....                    |     |     |                              |                       |                          |                                    |                       |                   | 17.7                       | 10.6   | 13.6                                     | 13.6                                  | 8.9                                   |   |
| Severe postoperative reactions   |     |     |                              |                       |                          |                                    |                       |                   |                            |  |  |                                       |                                       |   |
| 16                               | F   | 45  | 1                            | 46                    | No                       | 18                                 | 19                    | Hemi              | 15.8                       | —  | 15.1                                     | 12.1                                  | 10.0                                  | Second stage<br>case 2                            |
| 17                               | M   | 42  | 6                            | 80                    | No                       | 16                                 | 1                     | Hemi              | 23.1                       | 14.4   | —  | 10.4                                  | 10.1                                  |   |
| 18                               | M   | 42  | $\frac{1}{2}$                | 62                    | No                       | 26                                 | 21                    | Hemi              | 14.7                       | 10.6   | 13.1                                     | 10.9                                  | 11.1                                  |   |
| 19                               | F   | 50  | —                            | 45                    | No                       | 28                                 | 38                    | Sub-total         | 20.0                       | 22.2   | 27.0                                     | 21.6                                  | 16.0                                  | First stage<br>case 22<br>Second stage<br>case 21 |
| 20                               | F   | 41  | —                            | 57                    | No                       | 13                                 | 21                    | Sub-total         | 15.8                       | 12.2   | 17.8                                     | 20.0                                  | 12.5                                  |   |
| 21                               | F   | 36  | $\frac{1}{4}$                | 83                    | No                       | 19                                 | 37                    | Hemi              | 19.8                       | 14.4   | —  | 17.2                                  | 16.0                                  |   |
| 22                               | F   | 36  | $\frac{1}{2}$                | 71                    | Yes                      | 48                                 | 41                    | Hemi              | —                          | 10.0   | 13.6                                     | 13.0                                  | 12.0                                  |   |
| Average .....                    |     |     |                              |                       |                          |                                    |                       |                   | 18.2                       | 14.0   | 17.3                                     | 15.0                                  | 12.5                                  |   |

studies. The reaction indicated as "mild" represented a very favorable postoperative course with minimal reaction and rapid convalescence. The "moderate" reaction included fever to about 100° F. or 101° F., moderate tachycardia and a more prolonged reactive phase. The "severe" group was those in whom a fairly stormy postoperative period was encountered with high fever, more rapid pulse rate, some agitation and usually requiring the use of parenteral fluids for several days. Even the cases listed under "severe" did not approach a real crisis and no deaths occurred in this series. We have not had the opportunity to carry out these studies in the presence of a true thyroid storm.

*Methods:* Blood was drawn from the antecubital veins by suction into bottles containing iodine free oxalate. Plasma was obtained by sedimentation or centrifugalization. All determinations were done in duplicate. If checks within 10 per cent were not obtained new determinations were set up. This required the drawing of at least 75 cc. of blood for each determination. Ten cubic centimeters of plasma were used for each determination. The plasma was dialyzed for 72 hours against running water in Visking cellophane casings. This was done even if no iodine was known to have been ingested and was, of course, necessary once iodine therapy had been begun. The contents of the cellophane casings were then analyzed for their iodine content by the method previously described. The experimental background for the validity of this method can be found in the publication quoted. The normal values for plasma iodine by this method do not exceed 8 gamma per 100 cc. of plasma.

#### DISCUSSION

This study is an attempt to add to our knowledge of the events in the period immediately following thyroidectomy. Ever since the earliest attempts at the surgical treatment of Graves' disease, surgeons have encountered inexplicably severe postoperative reactions. This reaction is dramatically impressive and has been described in the literature as a "thyroid storm," "thyroid crisis" or "postoperative toxic reaction." In the era before the routine use of preoperative iodine medication these unfortunate reactions were very frequent and in the hands of very competent surgeons it was not unusual to have mortalities varying between 10 and 20 per cent. Many of these deaths were due to thyroid crises which began within 24 hours after the operation and often ended fatally in another 24 or 48 hours. The typical history of a thyroid crisis is somewhat as follows. A patient is suffering from severe or moderately severe Graves' disease. The preoperative course is not very satisfactory. The patient fails to gain weight, the tachycardia persists and the basal metabolic rate fails to decline during iodine medication. Often there is extreme motor and psychic unrest. Appetite is poor and sleeplessness is prominent. Frequently there is diarrhea or vomiting or both. Mild manic states may supervene. With some uneasiness the surgeon decides to operate "to stop the progress of the disease" or he is induced to operate "as a life-saving procedure." The operation may be accomplished without incident or more frequently the tachycardia increases and the patient is returned to bed. Soon marked restlessness occurs and the tachycardia



becomes even more marked. After 12 hours or so the temperature has begun to reach alarming heights and then severe hyperpyrexia ( $105^{\circ}$  to  $108^{\circ}\text{F.}$ ) appears. There is marked restlessness and frequently acute mania. The patient becomes incontinent and lapses into coma. The pulse rate may reach 200 per minute and the diastolic pressure approaches zero. Death occurs from 24 to 72 hours after the operation. The usual treatment is the use of sedatives and the administration of iodine by the intravenous route. All observers are agreed that the prognosis in a fully developed crisis is extremely grave and it is doubtful whether any therapy is of much value once the thyroid storm has really begun. The only therapy so far which seems to have been of service has been prophylactic. Operation should never be performed as an emergency procedure and should be done only when the patient's disease has been held in check by medical means and iodine. Most clinicians are aware of this now and the incidence of post-operative thyroid storms has diminished almost to the vanishing point in many clinics.

*The nature of the thyroid storm:* Because of the fact that these reactions usually followed operative procedures upon the thyroid gland it was generally believed that the crisis represented some acute augmentation of thyroid activity possibly as a result of mechanical expression of thyroid secretion into the circulation during operative manipulation or absorption from the wound bed. That such an inoculation of the blood stream may occur has been suggested by the recent studies of Lerman (2) who found a positive precipitin reaction for thyroglobulin in the blood from the thyroid vein only after trauma to the gland. On the other hand crises have occurred in patients with Graves' disease following operations far from the thyroid gland, such as pelvic operations, tonsillectomy or even the injection of varicose veins of the legs. In fact, not infrequently, we observe such thyroid storms while the patients are still on the medical wards being prepared for surgery. These "medical storms" are almost always ushered in by one of the acute upper respiratory infections to which these patients are so susceptible. Although the obvious stimulation that occurs during a crisis has led most observers to suspect an acute intoxication as the cause of the symptoms this view has not been the only one entertained. As early as 1925 Kessel and Hyman (3) recommended the intravenous use of thyroxine to combat the effects of the thyroid storm on the assumption that the sudden withdrawal of the thyroid secretion might lead to acute symptoms in patients previously established on a high level of hormone. In 1931 Bier and Roman (4) published a few cases in which they reported that there was a postoperative drop in the blood iodine level and they attributed the postoperative reaction to this and called it "Hypothyroxaemischer Schock." Gutzeit and Parade (5) obtained results in direct contradiction to those quoted above. The methods for the determination of iodine available to all these authors at those times must now be considered too inaccurate to warrant the conclusions drawn.

We are aware that the sudden withdrawal of the secretion of a hyperfunctioning gland may lead to acute symptoms. The occurrence of tetany following the removal of a parathyroid adenoma and of acute adrenal insufficiency follow-

ing removal of an adrenal cortical tumor are well known. However, in these instances the symptom complex produced is that which is well recognized as due to a deficiency of the particular gland studied. In the case of the thyroid storm an entirely new clinical picture is produced which has no relation to the phenomena of thyroid insufficiency as we have come to know them. It must be stated that the explanation of the thyroid storm as an acute thyroid insufficiency has not been established.

Others have sought in the central nervous system, particularly in the diencephalon, for the precipitating factor in the genesis of the thyroid storm. Morphologically, at least, there has been no evidence that the nervous system is primarily involved. Certainly no significant changes of an etiologic nature have been demonstrated in the brain to account for the explosive reaction we call a storm, nor in fact, have any significant, constant changes which have etiologic importance been found in the central nervous system in Graves' disease. We agree with Foss and his co-workers (6) that although the liver and the heart are involved in Graves' disease neither of them play an etiologic role in the development of the thyroid storm.

#### COMMENT

A study of the protocols reveals the following:

1. The blood iodine is uniformly increased in untreated Graves' disease of recent or old origin, and is a useful diagnostic aid.
2. Treatment with iodine tends to lower the level of the plasma iodine coincident with clinical improvement and in some cases such treatment restores the iodine level to normal.
3. There is an increase in the level of the plasma iodine immediately after thyroidectomy. This increase begins to disappear 24 hours after operation and reaches normal levels in uncomplicated cases 72 hours after the operation.
4. There is a definite correlation between the severity of the postoperative reaction and the course of the plasma iodine response. The more severe the reaction the greater and more prolonged was the rise in plasma iodine.
5. These studies lend support to the concept that the postoperative reaction in Graves' disease is, in part at least, due to the introduction into the circulation of excessive amounts of thyroid hormone as a result of the surgical procedure.

#### SUMMARY

Twenty-two cases of Graves' disease were studied. The plasma iodine (non-dialyzable) fraction was found to be elevated in all. The plasma iodine level decreased after treatment with iodine coincident with clinical improvement and sometimes reached normal levels. A definite correlation was found between the clinical severity of the postoperative reaction and the plasma iodine level in the postoperative phase. The more severe the postoperative reaction, the greater and more prolonged was the rise in plasma iodine. In uncomplicated and favorable cases the iodine level at the end of 24 hours reached or fell below the preoperative value and at the end of 72 hours was within the normal range.

There was no correlation between the basal metabolic rate and the initial plasma iodine level or between the initial plasma level and the degree of postoperative reaction but it seemed that patients with high preoperative iodine levels were more often subject to severe postoperative reactions than were those with lower plasma iodine values. It is suggested that the postoperative reaction in Graves' disease may be directly connected with the increase in plasma iodine (protein bound) which follows thyroidectomy. No real thyroid storm was encountered in this series.

## BIBLIOGRAPHY

1. SILVER, S.: *J. Clin. & Lab. Med.*, 28: 329, 1942.
2. LERMAN, J.: *J. Clin. Investigation*, 19: 555, 1940.
3. KESSEL, L., AND HYMAN, H. T.: *J. A. M. A.*, 84: 1720, 1925.
4. BIER, A., AND ROMAN, W.: *Ztschr. f. klin. Med.*, 118: 15, 1931.
5. GUTZEIT, K., AND PARADE, G. W.: *Ztschr. f. klin. Med.*, 135: 158, 1938.
6. FOSS, H. L., HUNT, H. F., AND McMILLAN, R. M.: *J. A. M. A.*, 113: 1090, 1939.

# POSSIBLE POSTWAR MALARIA OUTBREAKS IN THE UNITED STATES

## FACTS AND FALLACIES

### I. SNAPPER

The possibility of the establishment in the United States of certain exotic diseases which may be introduced by Army and Navy personnel returning from endemic areas abroad has long since had the attention of the responsible authorities. Among these diseases, malaria has been frequently mentioned.

From a historical standpoint it cannot be denied that the possibility of a post-war extension of malaria in the United States exists as malaria outbreaks have often followed in the wake of wars. At the moment there are different reasons for concern. They consist mainly of the concentration of troops for training in the southern areas of the United States where malaria is endemic and especially the wide distribution of American troops in malarious subtropical and tropical regions. It is certain that a considerable number of returning soldiers will suffer from malaria and the opinion has been voiced that in the United States where a malaria-carrying mosquito, the *Anopheles quadrimaculatus*, prevails, these malaria carriers may form a cause for severe outbreaks of malaria. In order to discuss this problem it will be necessary to analyze different factors which are contributory to the causation of malaria epidemics.

Malaria is a disease caused by plasmodia living in the red blood cells and transmitted from man to man by female anopheline mosquitoes.

It follows that a malaria epidemic depends upon the presence of

- a. a large number of proper mosquito vectors,
- b. a certain number of people parasitized with sexual forms of the malaria plasmodia.

For the problem of a possible postwar extension of malaria in the United States, the significance of these two factors *a.* and *b.* has to be discussed separately.

#### *a. Influence of the mosquito population on the outbreak and severity of malaria epidemics*

The characteristics of the mosquito population form far the most important factor which decides the malariousness of a certain area. Changes of the mosquito population followed by malaria outbreaks may be caused by

(1) a qualitative factor, i.e., the introduction of a new anopheles species which is a more active vector than the mosquitoes previously prevailing in an area.

(2) a quantitative factor, i.e., a change in the physical conditions of the country leading to improved breeding conditions for malaria mosquitoes and hereby to an increase of the malaria-carrying mosquito population.

*Ad (1).* One of the most recent and clear-cut examples of a malaria outbreak due to the introduction of a new and actively malaria transmitting

*Anopheles* species is the serious malaria epidemic which raged in Brazil in 1938 due to the introduction of a new malaria carrier, *Anopheles gambiae*, into that country (1, 2). Previous to this epidemic, malaria was endemic in Brazil in a chronic, not too dangerous form, transmitted by three different anophelines, all members of the *Nyssorhynchus* group. *Anopheles gambiae*, which is the common malaria vector in Africa, reached Brazil in 1930. The mosquito traveled probably on board of one of the French destroyers which made the mail run of about 2,000 miles between Dakar in Africa and Natal, the State capital of Rio Grande do Norte, in Brazil in less than 100 hours. In 1931, an organized campaign resulted in the eradication of *A. gambiae* from Natal but in the meantime this mosquito had already found a footing in the interior of Rio Grande do Norte. In 1937, the anopheles reached the Assí and Apodí valleys of this province and the Jaquaribe valley in the State of Ceará. Here, breeding conditions were favorable and in 1938, an epidemic of malaria developed which threatened large areas of these two States with wholesale devastation. In one area of the State of Rio Grande do Norte, 51,000 cases of malaria occurred among 243,700 inhabitants. This form of malaria was remarkably dangerous because in the first six months of 1938, at least, 14,000 deaths were recorded on 100,000 cases. Whole households were wiped out. In the most heavily stricken areas of the Jaquaribe valley 90 per cent of the population, both rural and urban, were ill. This fulminant epidemic of malaria in Brazil ranked with the classical epidemics that decimated Mauritius in 1867, the Punjab in 1908 and Ceylon in 1935—all comparable in their disastrous results with a cholera or plague epidemic. The epidemic in Brazil was only stopped when *A. gambiae* was completely eradicated by a meticulous anti-gambiae campaign organized by the Rockefeller Foundation in cooperation with the Brazilian Government. The extent of this campaign can be measured by the money spent on it, amounting to \$1,275,000 in 1939 and 1940. Since then malaria in Brazil has returned to the chronic, not too dangerous, endemic form which has existed there for scores of years.

Comparable is the experience in British and Dutch Guiana which are situated in the northern part of the East coast of South America. The coastal zone of Dutch Guiana on Surinam consists of recent deposits of clay, shell and sand. It is covered with swampy forests and near the coast line with reed swamps. The vast interior of the country consists of thick forests with a luxurious jungle vegetation. Between the coastal area and the interior a gently rolling Savanna belt is situated. In Surinam malignant malaria is rampant in the interior, in the so-called bush region. The vector in the interior is the *A. darlingi*. Every time this *A. darlingi*, for unknown reasons, invades the coastal area, a severe outbreak of malignant malaria follows (3). When either as the result of anti-mosquito measures or spontaneously, the *A. darlingi* retreats into the interior, the common mosquito of the coastal area, *A. tarsimaculatus*, again becomes the dominant vector of malaria in the coastal area and the malaria endemic of the coast recovers its benign and chronic character.

Such illuminating experiences explain the apprehension of the public health authorities concerning the possibility of the introduction of dangerous malaria



vectors into the United States. The following experience illustrates that the strict anti-mosquito measures taken at airports when airplanes from malarious regions arrive are completely justified. On October 9, 1941, one year after the eradication of *A. gambiae* in Brazil had been successfully terminated, a female *A. gambiae* was found on a flying boat which had arrived at Natal after a 21-hour flight from Lagos in West Africa. It may be said that the mosquito quarantine and the disinsectization of the aeroplanes in the United States airports is so rigorously maintained that for all practical purposes introduction of new anophelines into the United States seems well-nigh excluded.

For completeness sake it may be added that these measures not only protect the country against introduction of dangerous malaria vectors but at the same time against the import of other dangerous, possibly infected insects. The transfer of *Aedes aegypti* infected with yellow fever from Africa or South America into the United States might well result in a calamity. It would probably lead to the reappearance of summer epidemics of yellow fever in the southern United States where *Aedes aegypti* is permitted to breed unrestrained.

*Ad (2).* Apart from the introduction of a new malaria mosquito, the increase of the indigenous anopheles population by a change in the physical conditions of the country has often been a cause for the outbreak of dangerous malaria epidemics. Here, the experience of the malariologists of the Netherlands East Indies may be mentioned. In this territory which belongs to the most malarious regions in the World, a few coastal areas are practically malaria-free. This holds true for the broad zones of swampy mangrove forests which blur the boundary between land and sea on certain parts of the muddy shores of Sumatra but especially of Borneo. Forests of mangroves—tropical trees with aerial roots are only found on coasts where a heavy tide is running and in these deeply shaded forests the extreme differences between high and low tide prevent the breeding of the indigenous malaria mosquitoes. This explains why sea coasts covered by mangrove forests are often relatively malaria-free. The public health expert who travels in these regions may, at first view, be unfavorably impressed by the aspect of the cities intersected by muddy canals as found on the mangrove shores. But even so, such cities as Bandjermasin and Martapoera on Borneo have only a low incidence of malaria because the muddy city canals are constructed in such a way that the tide has free entrance. Hereby these canals are prevented from becoming breeding places for malaria-carrying anophelines.

However, as soon as the mangrove forests are felled, and dykes are constructed for cultural purposes, swampy areas, which cannot be reached by the tide, result. These pools form an excellent breeding place for the indigenous mosquito, *Anopheles sundaicus*, which prefers saltwater pools with not too much shade for its breeding places. The ensuing increase of the *Anopheles sundaicus* population is immediately followed by an acute malaria outbreak.

Man-made malaria is also found in Dutch New Guinea where *A. punctulatus moluccensis* and *A. punctulatus punctulatus* are the most important malaria vectors. Both are obligatory sunbreeders. As long as the original forests of

New Guinea are left intact, malaria is bad enough, partly due to *Anopheles bancrofti* which breeds in the shadow. When, however, the trees are felled without simultaneous careful and minute drainage of the soil, the two sunbreeders mentioned multiply without restraint. These strains of *A. punctulatus* are more effective malaria carriers than *Anopheles bancrofti* and an acute malaria outbreak results.

In the same way, felling of forests causes malaria in hilly areas of Malaya and the western part of the Netherlands East Indian Archipelago where *Anopheles maculatus* or other sunbreeders act as malaria vectors. Often man-made malaria is caused inadvertently and new experiences are collected as public health in the tropics develops. The following example illustrates how complicated these conditions may be.

The Netherlands East Indies had always been free from plague until 1911 when a serious epidemic broke out on the island of Java. Study of the epidemiology of the plague in Java showed that the plague bacillus reservoir in Java consists of the Malayan house rat, *Rattus rattus diardi*, which builds its nest in the dark, especially in horizontal bamboos, on roofing poles and ceilings, in palm leaf thatched roofs, in the native bamboo bedsteads (the so-called balé-balé), in piles of timber, and stores of food. This rat species fortunately has no tendency to migrate; thus the epizootic of the rats is held in bounds. The importance of the structure of houses as breeding places for rats is indicated by the prevalence of plague among the Indonesians in the very villages and cities where the Chinese and Europeans who live in houses built from other material remain practically free. This explains why extensive schemes for the improvement of houses and careful supervision of the building of new houses have played a major role in the anti-plague campaign in Java. When houses were newly built or improved, the use of hollow bamboo which, as mentioned above, favors the breeding of rats, was strictly forbidden. The following principles were used for the improvement of the houses.

- (1). All thatched roofing was replaced by tiles or corrugated iron.
- (2). All unsplit, hollow bamboo was
  - (a) wherever possible, replaced by wood.
  - (b) where wood was scarce, wooden stoppers were inserted into the ends of the bamboo.
- (3) All parts that cannot easily be seen (i.e. pieces between two layers of open bamboo) were eliminated.
- (4) The square ridge pole was turned in at an angle so that no rat nests could be built upon it.

By the beginning of 1940, 1,579,753 houses had been improved and 962,400 houses had been built under the supervision of the antiplague service. This campaign for the construction of improved houses has been one of the main factors in stopping the plague epidemic. However, in the same area, where thanks to this improvement of housing conditions, the plague mortality decreased, the general mortality increased. This increase of the general mortality rate was due to a malaria epidemic which practically always followed within a

few months after the houses had been improved. The improvement of the dwellings transformed the very undesirable huts of the Indonesians into neat little houses with tiled roofs. The kitchen, which in the original huts was combined with the living room, was in the improved house located outside the dwelling. A smoke-catching device provided excellent ventilation, and there was not the slightest doubt that the new houses had much more light and more air than the old native dwellings. Unfortunately, the absence of smoke in the house permits mosquitoes to enter the dwelling. Mosquitoes, in general, abhor smoke. At the same time, smoke hides the odor of the human body; and when no smoke is present, the human body odor attracts the anophelines. Careful counts have shown that ten times as many mosquitoes were found in the improved houses than in the old unhygienic Indonesian huts. Most of these extra mosquitoes were proved to be the dangerous malaria carrier, *Anopheles aconitus*, a situation which explains the spread of malaria, following the improvement of dwellings.

This unexpected and highly undesirable complication of the house improvement campaign is another example of man-made malaria. It shows how carefully any interference with the customs and ways of life of a native population must be weighed, because undesirable side effects of hygienic improvements often turn up unexpectedly.

Even in nontropical regions the danger of manmade malaria exists. In the Netherlands (4) the malaria vector is *A. labranchiae atroparvus* which needs for breeding purposes:

Brackish water,

A horizontal water vegetation and,

Narrow water sheds with a maximum width of three feet.

This explains the remarkable experience that in the northwestern part of the Netherlands reclaiming and draining of pools and swamps have often resulted in a malaria outbreak. The large surface area of the original pool was unfavorable for the breeding of *A. atroparvus*. The narrow irrigation ditches, however, which remained after the land had been reclaimed, formed a favorable breeding ground for the anopheles and a malaria outbreak resulted.

Other examples of man-made malaria could easily be cited. As far as the United States are concerned, our knowledge of the breeding habits of *Anopheles quadrimaculatus*, i.e., the vector of malaria in the United States, is highly satisfactory. For a campaign against this special mosquito, drainage is the all important factor supplemented by filling in of marshy areas and extension of pumping facilities. In all artificial irrigation plots, the excess of water must be carefully removed. Improvement of natural channels and streams, supervision of artificial ditches, pits and culverts are efficient means of the campaign against *Anopheles quadrimaculatus*.

On the basis of this knowledge civilian and military authorities have put a comprehensive program for the control of malaria and mosquitoes into effect throughout the United States (5). The Army has made large expenditures in 1942 to control malaria among troops living in permanent stations in the Con-

tinental United States. Thanks to this program the malaria rate among the troops in this continent has gone down to 60 per 100,000 per year—the lowest rate ever recorded by the Army although the number of troops training in the malarious areas of the southern States is larger than ever. This campaign has been assisted and supplemented by extra-military mosquito control work of the United States Public Health Service.

It may thus be said that the United States has guarded carefully against danger of a sudden increase of the anopheles population due to a change in the physical characteristics of the country. Considering the emphasis that has been placed on the control of malaria in this country, it is inconceivable that any construction or reclamation projects would be permitted which would be conducive to the development of epidemics of man-made malaria. Even so, it must be recognized that in any locality a suitable breeding place for mosquitoes may be created inadvertently and constitute an actual or potential source for the local spread of malaria.

*b. Influence of the number of human malaria carriers on outbreaks.*

It is generally accepted that if the quota of the population which is parasitized with sexual forms of malaria plasmodia descends to below one to two per cent, the malaria endemic stops automatically. It must thus be discussed whether the reverse is also true: will the increase of the malaria carriers in the United States, which will result from the return of the Army and Navy personnel especially from the Pacific area, give rise to a malaria outbreak? Fortunately, experiences collected all over the World indicate that the introduction of virulent strains of malaria plasmodia from other areas is hardly a factor of importance for the causation of acute malaria outbreaks.

There exist considerable differences in the virulence of different malaria strains—not only in the estivo-autumnal type of malaria but also in the tertian type. Malaria in the Netherlands, for instance, is always a very benign form of tertian malaria. It is characterized by an exceedingly long incubation period. In Holland, human infection by *A. labranchiae atroparvus* takes place in August and September but fever only develops in the spring of the following year. On the other hand, tertian malaria in the Netherlands East Indies is very virulent. It must be considered certain that repatriating malaria patients from the Dutch territories in the Far Orient continuously introduced virulent tertian strains into the Mother Country (Holland) but this has never led to the occurrence of malignant malaria. Occasional malaria epidemics in the Netherlands could always be ascribed to increase of the mosquito population due to reclamation projects, building of new city boroughs, etc.

In Dutch Guiana the coastal district of Nickerie is nowadays free from malaria although *A. tarsimaculatus* is present in abundance. Every year travelers from the interior of Surinam return to Nickerie, suffering from severe tertian, and often from estivo-autumnal malaria, but notwithstanding the presence of the vector, *A. tarsimaculatus*, major outbreaks of malaria have not occurred since 1926.

On the island of Curaçao in the Caribbean, no malaria occurs. Still a pos-

sible vector, *A. pseudopunctipennis*, is present and every year hundreds of people from Surinam immigrate into Curaçao, many of whom are malaria carriers. Similarly in the United States, malaria vectors have been identified far up the Mississippi and Ohio River Valley and even though persons with malaria have come into these regions, the disease has not succeeded in establishing itself.

In Portugal several highly malarious areas are found, especially in the rice-growing regions of the country (6). Every year thousands of laborers, often even the inhabitants of entire villages, travel long distances to help harvest the rice crop. They are lodged in unhygienic temporary dwellings, close to the rice fields, and practically all of them become infected with malaria. After the harvest is over they return to their own villages, often located in malaria-free parts of the country. Although anophelines capable of transmitting malaria are found all over Portugal, these returning malaria carriers do not cause acute outbreaks in their home villages. This holds true even for Aveiro in north-western Portugal near the mouth of the Vouga River where the anopheles population is dense but where anophelines have little tendency to invade human habitations.

On the basis of these and other comparable experiences the danger of the introduction of virulent strains of malaria in the United States as the result of the return to this country of Army and Navy personnel harboring these parasites is considered to be negligible.

#### SUMMARY

Acute malaria outbreaks may be favored by different conditions.

a. Introduction of a new active anopheline carrier has often proved to be the causative factor of a malaria epidemic. The United States is well protected against this contingency by the strict antimosquito quarantine which is organized at all airports where airplanes from malarious regions arrive.

b. Changes of the physical characteristics of an area have often resulted in improved breeding facilities for mosquitoes. The ensuing increase of the malaria-carrying anopheline population has then been followed by an acute malaria outbreak. The Army and Public Health authorities of this country have by a nationwide campaign reduced the mosquito breeding areas to a minimum and careful legislature bars construction or reclamation projects which could lead to improved anopheles breeding facilities and to outbreaks of man made malaria. Therefore, the country is well protected against this danger too.

c. There remains the fact that when the Armed Forces return, the number of persons carrying sexual forms of malaria plasmodia in their peripheral bloodstream in the United States will be considerably increased. Experiences collected all over the World indicate that in case the two factors mentioned under a. and b. are well controlled, an increase in the number of malaria carriers does not cause acute malaria outbreaks.

It may thus be foreseen that as long as the public health measures against malaria are carried on, the United States does not need to fear malaria outbreaks resulting from the return of Army or Navy personnel infected with malaria.



## BIBLIOGRAPHY

1. SOPER, F. L., WILSON, D. BRUCE: Species eradication. J. Nat. Malaria Society, 1: 5, 1942.
2. SOPER, F. L., WILSON, D. BRUCE: *Anopheles gambiae* in Brazil 1930 to 1940. New York City, The Rockefeller Foundation, 1943.
3. SWELLENGREBEL, N. H., VAN DER KUYP, E.: Health of White Settlers in Surinam. Colonial Institute at Amsterdam, 1940. Special Publication No. 54.
4. SWELLENGREBEL, N. H., DE BUCK, A.: Malaria in the Netherlands. Amsterdam. Scheltema & Holkema, 1938.
5. SIMMONS, J. S.: Progress in the Army's fight against malaria. J. A. M. A., 20:30, 1942.
6. SIMMONS, J. S.: The Present State of the Army's Health, J. A. M. A., 122:916, 1943.

## THE ROENTGEN DIAGNOSIS OF DILATATION OF THE PULMONARY ARTERY

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The roentgen diagnosis of pulmonary artery dilatation ordinarily is based upon the appearance of the "pulmonary artery segment" of the left cardiac contour which is caudad to the "aortic knob" and cephalad to the left auricle or auricular appendage, the latter being cephalad to the left ventricle. Elongation and increased density of this segment with a bulging convexity to the left in the postero-anterior view, exaggerated when the patient is rotated into the right anterior oblique position, is the main finding. An enlarged dense, circular shadow seen through the "aortic window" in the left anterior oblique position particularly when associated with a thickened left main branch, as well as an exaggerated pressure defect on the oesophagus seen best in the right anterior oblique position, are regarded as confirmatory signs. Assmann and Zdansky (1) state that increased width of the right hilum is an indication of generalized pulmonary artery dilatation. A dilated pulmonary artery often is found to pulsate more actively than usual and, when the pulse pressure is increased and particularly when pulmonary insufficiency is present, the pulsation may be of the "collapsing type" (hilar dance).

A classification of the conditions which may be associated with pulmonary artery dilatation has been made by Assmann (1) and by Roesler (4). Schwedel and Epstein (5) discuss the value of the roentgen examination in evaluating the size of the artery and refer to the fact that dilatation of this vessel may follow right ventricular hypertrophy and dilatation. Brown, McCarthy and Fine (2) emphasize the value of roentgen kymography in the study of this vessel. Parkinson (3) considers prominence of the pulmonary artery segment to be an indication of right ventricular dilatation in emphysema. The present authors have discussed this subject as well as the cardiac contours in mitral disease in previous publications (7).

A review of the literature discloses that there has been no emphasis on the disparity in many cases between the roentgen and the anatomical findings nor has there been evaluated the precise contribution of the pulmonary artery to the contour ordinarily considered to represent it. There has been only occasional reference to the fact that the pulmonary artery may be dilated in the absence of significant roentgen abnormalities (6) although Roesler (4) states clearly that "disease of the pulmonary artery or its branches may not be disclosed by roentgenologic study." Per contra, prominence of the pulmonary artery segment in the absence of anatomical dilatation has been widely recognized as, for example, in thyrotoxicosis and in the heart of adolescent asthenics. In some of these, functional dilatation has been postulated but proof is lacking.

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The present report proposes, through case demonstration, to emphasize the unreliability of the roentgen examination in the *positive* diagnosis of dilatation or lack of dilatation of this vessel. The angiocardigraphic method provided the means for precise analysis of the pulmonary artery segment of the left contour. These cases also illustrate that there is no necessary correlation between dilatation of the pulmonary artery and enlargement of the right ventricle.

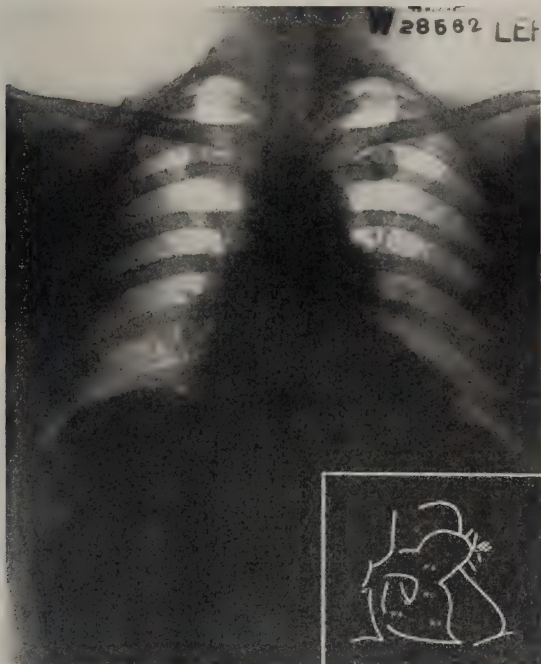
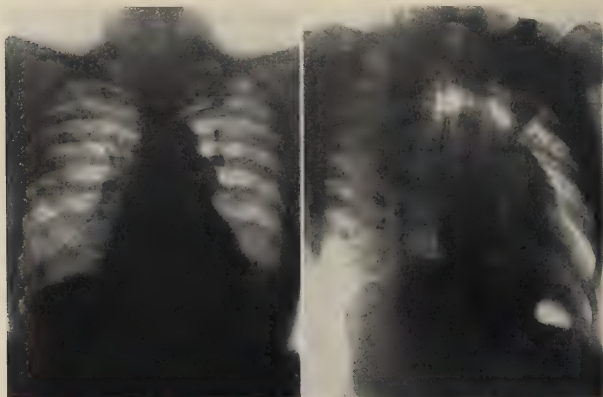


FIG. 1. Leutic dilatation of the pulmonary artery (P.A.). The "pulmonary artery segment" is formed by the left pulmonary artery. The location of the pulmonary conus (P.C.) and right ventricle (R.V.) are indicated.

*Case 1.* Probable leutic involvement of the Pulmonary Artery was found in a 52 year old man who was observed for several years in the venereal clinic. He had no subjective complaints but a positive Wasserman was discovered. Radiographic examination of the chest revealed moderate enlargement of the heart to the left. The aorta seemed of normal size. A localized bulge of the pulmonary artery segment was seen. Angiocardigraphy, however, demonstrated that this bulge represented the lateral margin of the peripheral portion of the left main branch. The markedly dilated main artery and the degree of dilatation of both

main branches were unsuspected. This case emphasizes the marked discrepancy that can occur between the radiographic appearance and the actual extent of the disease. The



a



b

FIG. 2a: Idiopathic dilatation of the pulmonary artery, postero-anterior and right oblique positions. Note prominent pulmonary artery segment.

b: Angiocardiograph in the left oblique position (on the left) and a tracing of the angiocardiograph in the postero-anterior position (on the right).

pulmonary artery and most of its left main branch do not contribute directly to the contour upon which the diagnosis ordinarily is based. There did not appear to be any significant enlargement of the right ventricle.

*Case 2. Idiopathic dilatation of the Pulmonary Artery.* The patient suffered from no cardiac symptoms. She was treated and observed for recurrent neurodermatitis of mild degree in the Skin Clinic. Physical examination revealed a short faint diastolic murmur at the pulmonic area. Radiographic examination in the postero-anterior view revealed no prominence of the pulmonary artery segment although the left pulmonary artery seemed of an unusual shape. The right anterior oblique view revealed a considerable degree of

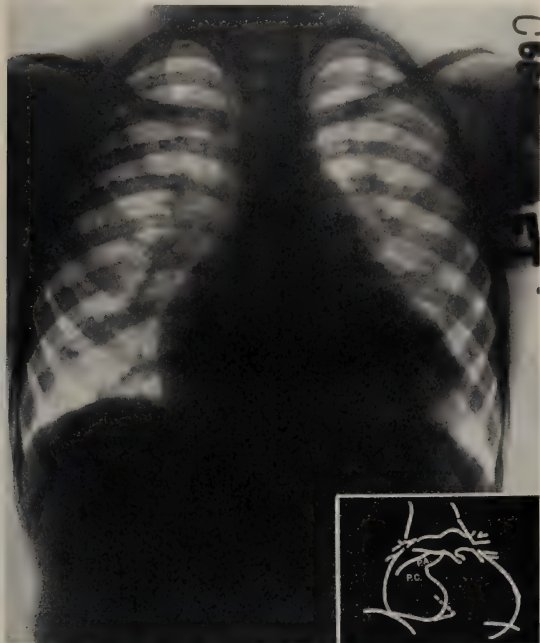


FIG. 3. Interatrial septal defect. The pulmonary artery segment represents the left pulmonary artery. The pulmonary artery itself is hidden in the cardiac shadow and is displaced to the right.

prominence of the pulmonary artery segment; there was no left auricular enlargement. Angiocardiographic examination revealed a markedly dilated pulmonary artery without definite evidence of right ventricular enlargement although the ventricular apex was perhaps slightly rounded. The discrepancy between radiographic appearance in the postero-anterior view and actual size of the pulmonary artery was marked. The oblique views, however, were accurate in their indication of the size of the vessel.

*Case 3.* The patient, a boy, aged 6 years, had clinical findings suggesting *interatrial septal defect*. Angiocardiography indicated the presence of a large left auricle and ventricle.



Moderate enlargement of the right ventricle and right auricle were present. The pulmonary artery was of normal size or might be regarded as slightly hypoplastic. Prominence of the pulmonary artery segment which appeared in the conventional postero-anterior view



FIG. 4. Isolated pulmonic stenosis. Although the pulmonary artery is moderately dilated it is the apposition of the left pulmonary artery which produces the elongated convex pulmonary artery segment.

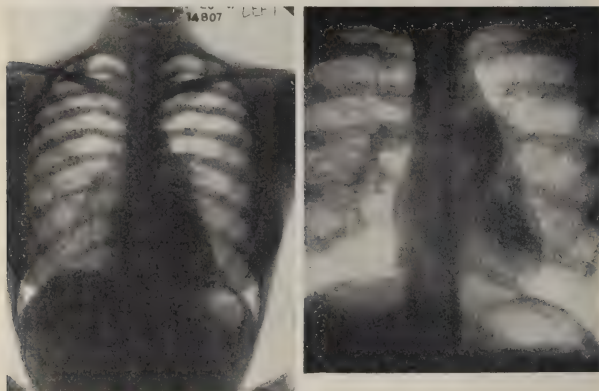


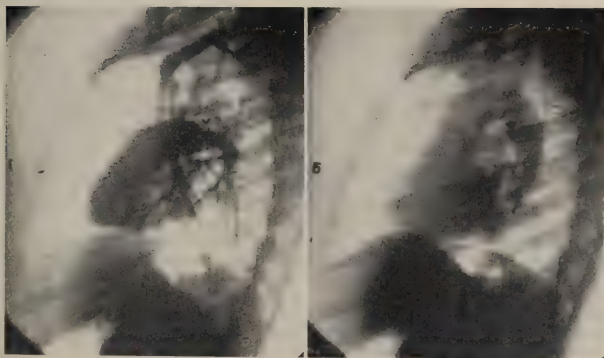
FIG. 5. "Adolescent Heart." Angiocardiograph (on the right) shows the pulmonary artery of normal size but so disposed as to produce a prominence of the pulmonary artery segment.

apparently was due to upward displacement of the pulmonary artery segment resulting from enlargement of the left auricle and the right ventricle but not to pulmonary artery dilatation.

*Case 4.* This patient, a girl aged 8 years, suffered from *isolated pulmonary stenosis* which was confirmed by angiocardiographic examination. The middle segment of the left cardiac



a



b

FIG. 6a: Patent ductus arteriosus (postero-anterior view).  
 b: Angiocardiograph (on the left) shows moderate dilatation of the pulmonary artery. Metal clips are seen on the ductus. The pulmonary artery is drawn cephalad and posteriorly by the short ductus. On the right the infundibulum of the ductus is seen extending from the inner border of the proximal descending aorta just caudad to the metal clips.

contour showed marked prominence. Considerable right ventricular enlargement was found by angiocardio-gram but only a moderate degree of pulmonary artery dilatation beyond the stenosed valve. The prominent middle segment was seen to be produced by the left pulmonary artery which, in this case, had a more lateral than posterior direction. The precise analysis of the "pulmonary artery segment" was possibly only by angiocardio-graphy.

*Case 5. "Adolescent Heart."* This patient, an 18 year old female, was considered for many years as suffering from congenital heart disease. Intensive re-investigation of the case failed to reveal any evidence of intrinsic cardiac disease. The patient was of asthenic build with a flat chest. The pulmonary artery segment was prominent in the postero-anterior view. The heart appeared somewhat enlarged to the left but oblique and lateral views demonstrated that the postero-anterior diameter of the heart was small.

Prominence of the pulmonary artery segment in asthenic individuals is quite well known. Angiocardio-graphic examination in the present case demonstrated that it was not due to pulmonary artery dilatation but to the high position and unusual course of the adjacent left pulmonary artery. The latter probably is to be attributed to the abnormal configuration of the chest.

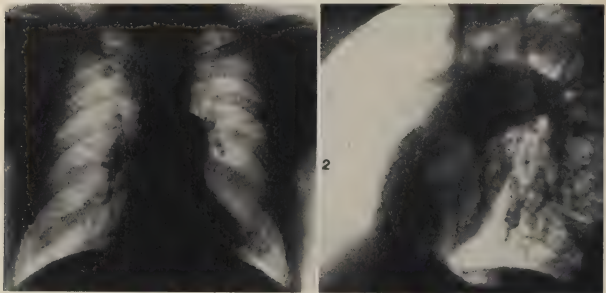


FIG. 7. Idiopathic dilatation of the pulmonary artery, with normal size right ventricle.

*Case 6.* The patient, a girl aged 11 years with *patent ductus arteriosus* proved by angiocardio-graphy and subsequent ligation. Considerable prominence of the pulmonary artery segment was associated in this case with a mild degree of pulmonary artery dilatation. In *patent ductus arteriosus* with a short ductus, the pulmonary artery is drawn upwards towards the isthmus of the aorta. This explains the frequent finding of a prominent pulmonary artery segment without pulmonary artery dilatation. Hence prominence of the pulmonary artery segment is not necessarily an indication of the size of the pulmonary artery in this disease. Furthermore, since right ventricular enlargement usually is absent in *patent ductus arteriosus*, the size of the pulmonary artery gives no indication of the size of this chamber.

*Case 7.* The patient, a 37 year old male, was completely asymptomatic. There was no relevant past history. The prominent pulmonary artery segment was discovered as the result of an x-ray examination made for employment. No significant murmurs nor electro-cardio-graphic changes were present. The marked prominence of the pulmonary artery segment in this case was due entirely to pulmonary artery dilatation as demonstrated by angiocardio-graphic examination. The right heart appeared to be normal although the demonstration was not clearly made.

## CONCLUSIONS

Seven cases are presented in which the "pulmonary artery segment" of the left cardiac contour did not accurately portray the size of the pulmonary artery. The discrepancy was due in some cases to the fact that the roentgen shadow of the left pulmonary artery merged with that of the pulmonary artery and its contour constituted the "pulmonary artery segment." In others, the pulmonary artery or its left branch were displaced as the result of an enlargement of a cardiac chamber or some extracardiac influence: the artery was not dilated at all or only moderately so. In one, a dilated pulmonary artery produced no abnormality in the "pulmonary artery segment."

These cases also demonstrated that prominence or convexity of the pulmonary artery segment cannot be taken as a definite indication of right ventricular enlargement. This conclusion would be justified only in the presence of clinical evidence of cor pulmonale.

## BIBLIOGRAPHY

1. ASSMAN, H.: Die klinische Röntgendiagnostik der Inneren Erkrankungen. Vogel. Leipzig. 1929.
2. BROWN, S., MCCARTHY, J. E., AND FINE, A.: Roentgenographic and roentgenkymographic Study of the Pulmonary Artery. *Radiol.*, 32: 175, 1939.
3. PARKINSON, J., AND HOYLE, P.: The Heart in Emphysema. *Quart. J. Med.*, 6: 59, 1937.
4. ROESLER, H.: Clinical Roentgenology of the Cardiovascular System. Illinois, Thomas. Springfield, 1937.
5. SCHWEDEL, J. B., AND EPSTEIN, B. S.: Radiological Study of the Pulmonary Artery with especial Reference to the main Bronchus. *Am. Heart J.*, 11: 292, 1936.
6. SUSSMAN, M. L.: Roentgen Examination of the Aorta and Pulmonary Artery. *Am. J. Roentgenol.*, 42: 75, 1939.
7. SUSSMAN, M. L., GRISHMAN, A., AND STEINBERG, M. F.: Angiocardiography in
  - (a) Right Heart Enlargement. *New England J. Med.*, 228: 777, 1943.
  - (b) Emphysema. *Am. J. Roentgenol.*, 47: 368, 1942.
  - (c) Mitral Disease. *Am. J. Roentgenol.*, 51: 33, 1944.

## PRECLINICAL AND SYMPTOMLESS PULMONARY TUBERCULOSIS

MAX TASCHMAN, M.D.

It is the x-ray that has made it possible for us to speak of preclinical, symptom-free or symptom-poor tuberculosis. It is not long since we were taught that the early symptoms of tuberculosis were: a cough that hangs on, fatigue, unexplained weight loss, slight fever, blood in the sputum. It is not long since a diagnosis of tuberculosis was greeted with suspicion in the presence of repeated negative microscopic findings. When the stethoscope reigned supreme, the finding of subcrepitant râles at one or both apices corroborated the diagnosis, but the absence of râles cast a suspicion of doubt.

If speed of progress bears any relation toward ultimate perfection, one might theorize that we are on our way toward a satisfactory solution of some perplexing contemporary problems by the speed of change in some of our ideas and methods, and simultaneously by the rapid obsolescence of others.

With the more intensive use of the x-ray, we became aware that sanatoria harbored cases that were not early, but many that were moderately advanced or advanced.

When it became apparent that symptomatic tuberculosis was not the early form—that the early case had few, if any, symptoms—that the symptomless patient presenting no complaints had no reason to consult a physician voluntarily—then began the search of the ideal case by extensive case finding surveys by means of the x-ray.

During the past decade or more, extensive case-finding campaigns have been conducted in various parts of the nation. Persons in all walks of life, chiefly between the ages of sixteen and thirty, have been examined by the x-ray. In New York City, several years ago, an intensive and extensive campaign was conducted by Dr. Herbert Edwards (1) Director of the Bureau of Tuberculosis, involving several hundred thousand cases. Among them were groups of high school boys and girls, young college students, skilled and unskilled workers, and on down to the scale of the irredeemable derelicts. Long ago it had been suspected, and later confirmed, that young children up to the age of thirteen or fourteen, though they may show signs of primary infection, seldom develop the clinical or adult type of disease. As one would suspect, the smallest number of positive x-ray findings of clinical disease were found in the high school group, about three in a thousand, and the largest number, about four and a half per cent, among the derelicts of the Bowery "flop houses" and municipal shelters.

A great stimulus favoring the discovery and evaluation of the preclinical type followed the enactment of the compensation law in New York State that went into effect September 1, 1937, declaring that an occupation that brings one in contact with the tuberculous is an industrial hazard, and the contraction of tuberculosis under these circumstances is an occupational disease. Nurses who acquired tuberculosis in the course of their training or practice in hospitals, became eligible for compensation benefits if the source of their illness could be



traced to their work. Before then, systematic x-raying or serial chest x-rays were seldom made of nurses. Some hospitals had a single x-ray throughout the entire period of training; others when the pupil nurse was admitted to training and when she was graduated; still others made them regularly once a year, and a few made them once in six months. There was no uniformity about it. Whatever the method these institutions pursued was wholly voluntary. Since the advent of the compensation law, serial chest x-rays are now made regularly at least every six months of all nurses, and some of the other hospital personnel in most of the tuberculosis institutions of this State. Since general hospitals inadvertently do admit tuberculosis cases for one reason or another, estimated by some at about 5 per cent, they, too, have inaugurated periodic x-ray chest examinations of hospital personnel who come in close contact with tuberculosis. Nurses developing tuberculosis anywhere in a tuberculosis institution or in a general hospital, can claim compensation if they can prove exposure to tubercle bacilli. At present, chest x-raying of the ward personnel in general hospital is not conducted methodically or in accordance with any set plan, and there is a movement on foot to make it obligatory for all general hospitals to provide chest x-ray examinations at stated intervals at least once every six months. In my experience, nurses who develop tuberculosis in any type institution, when they can prove exposure to an open case of pulmonary tuberculosis, almost invariably win their claim for compensation.

In my contact with nurses who developed tuberculosis as an occupational disease, the age of twenty three stands out as particularly hazardous. I can offer no valid explanation for this. A few were younger and some were older; very few developed the first adult lesion after the age of thirty-five. In my service at Riverside Hospital, where only graduate nurses are employed, an attempt has been made whenever possible, to employ nurses only who are thirty or more years of age.

Young girls admitted to training schools with a negative Mantoux test, sooner or later turn positive in the course of their training. The number of positives is progressive with each year of training. More city girls are positive than those from rural areas when they enter training. Sensitivity develops sooner in tuberculosis institutions or in general hospitals where open cases of tuberculosis are treated. Clinical disease may develop early, progress rapidly, and terminate fatally. A small infiltration in the x-ray film may appear innocuous but may prove serious. For this reason, nurses with a negative Mantoux test should not be accepted in the wards of tuberculosis hospitals. In general hospitals, where cases of open tuberculosis are encountered, young nurses admitted with negative Mantoux tests may turn positive early in the course of their training, and if exposed to repeated large doses of bacilli, may develop an acute form of tuberculosis instead of a simple primary complex. As a rule those who enter training with a positive Mantoux reaction are less susceptible to the development of clinical tuberculosis than the negative ones, fortifying our old conception that early childhood infection does confer a degree of immunity, slight as it is. A positive Mantoux case of long standing may show more resistance when an initial

clinical infiltration is discovered in the x-ray film than the recent positive Mantoux case. In the sensitized case of long standing, there is less tendency to early breakdown with cavity formation and spread of disease. It must be kept in mind that primary infection may occur among young people and these may emerge rapidly into the adult form with serious consequences.

Some colleges realize the importance of detecting the preclinical type of tuberculosis in their students. Some schools demand an x-ray film or the report of one with the initial application for admission. This precaution is the exception rather than the rule. Out of a large group of colleges studied recently, only about half employ routine x-ray examination on all student admissions. Some schools repeat the x-ray and some only recommend a film annually. There is no uniformity regarding this procedure in our higher centers of learning.

The induction of large numbers of young men and women into the armed services during the past two or more years, and particularly since Pearl Harbor, has revealed many symptomless cases who otherwise might have gone on to advanced disease.

In the global conflict now raging, a total of about twelve million young Americans, male and female, all at an age peculiarly susceptible to tuberculosis, have been inducted into the armed services following a preliminary negative x-ray chest film. These examinations, to my knowledge, have been conducted with extreme care, and it is doubtful if many clinically active cases escaped detection prior to induction. I have seen some rejections who showed no clinical tuberculosis whatsoever but only scars or evidence of primary infection. I mention this only to confirm the extra caution that was exercised in the selection of recruits, and yet active pulmonary tuberculosis is developing daily in the Army and Navy and many thousands have by now been hospitalized. Preliminary sensitivity tests were not performed since the exigencies of the moment made speed for mobilization a prime consideration. How many of these were primary or secondary infections only the future can tell. This large scale experiment may in time yield valuable information regarding the pathogenesis of the disease, the type of pathology encountered, the stage at which the disease was recognized and the results of treatment. Young men and women have been drawn from all walks of life, from city and rural areas, many doubtless from city areas who had previously become sensitized, and others from rural areas who had not. How will these two groups, urban and rural, sensitized and negative reactors, respond to their infection? How many now disabled acquired endogenous and how many exogenous infection? How many of them were diagnosed "early" and now many in whom the disease had already become well established with cavity formation and positive sputum? Since follow-up periodic x-rays in war time may not be regarded as a feasible procedure, diagnosis had to wait until the symptoms forced the patient to seek help and by this time physical signs, laboratory findings and the x-ray findings were sufficiently advanced to establish a diagnosis. These cases are not, therefore, the early cases we are seeking. I have seen several of these service men who are now under treatment for tuberculosis. All those I saw, and they are a limited number, revealed an exudative type lesion

that spread rather rapidly, limited more or less to part of a single lobe and showed very little fibrosis. Evidence of cavity was already distinct; all had a positive sputum and all were being treated with pneumothorax to which they responded favorably. The pathology as viewed in the x-ray film showed little chronicity, and one is justified in asserting that the process was a rather recent one.

In a study conducted on student nurses at Bellevue Hospital, H. M. Riggins and J. B. Amberson (2) reported positive roentgenographic pulmonary findings six times as frequent in tuberculin negative individuals as contrasted with the sensitized ones.

Similarly J. Heimbeck reports five times as many pulmonary lesions in non-sensitive tuberculin cases as compared with the sensitive group (3, 4). Leopold Brahdý (5) reporting on five training schools of municipal hospitals in New York City, states that clinical tuberculosis occurred six times as frequently in non-sensitized cases as compared to the sensitized ones.

That negative reactors in an environment highly charged with tubercle bacilli sooner or later become sensitized is a commonplace experience and a logical expectation. How many of these are instances of primary infection requiring none or a minimum of treatment; how many of them within a short interval proceed to the secondary or adult stage of disease with uncertain consequences; how many after a period of sensitization acquire a super infection by the endogenous route from a primary lesion that had not yet healed completely, and how many by an exogenous route due to contact or with the hazards of their employment, are some of the questions that presently baffle the keenest intelligence and for which no ready solution is at hand.

Preclinical lesions are found to be limited in over 90 per cent of cases, whereas patients *coming to physicians with symptoms* have limited lesions in only about 30 per cent, that is, 70 per cent are already in a moderately advanced or advanced stage. For years on end, a perusal of statistics of the stage of disease on admission to tuberculosis institutions, despite the advances in our knowledge of tuberculosis made in the interval, reveals the same sorry tale—30 per cent to 35 per cent are early cases, the balance fall in the more advanced categories.

#### CASE REPORTS

*Case 1.* A. S.; a thirteen year old boy, whose mother is ill with extensive pulmonary tuberculosis, cavity, positive sputum, and is receiving pneumothorax. One brother has tubercular glands in his neck, and two sisters show evidence of tuberculosis infection by a Mantoux test, but in them x-ray examination of the lungs was negative. The accompanying illustration (fig. 1) reveals an early infiltration in the third interspace adjacent to the heart. This is a symptomless case. Of significance is the fan-shaped distribution of the infiltration, a not uncommon occurrence in young persons.

*Case 2.* S. K.; seen by me for the first time on November 18, 1939. A seventeen year old high school girl, who was x-rayed in school five weeks before her visit to me. The x-ray showed a "spot on the lung." Her family history was negative. She had no complaints, and physical examination was negative. On x-ray examination she showed a fine exudative lesion in the second left space anteriorly and behind the third and fourth ribs adjacent to the root (fig. 2A). She was put to bed immediately; repeated sputum examinations were negative. In the course of six weeks of bed rest, a slight temperature up to



FIG. 1 (Case 1). Roentgenogram showing early infiltration in third interspace.

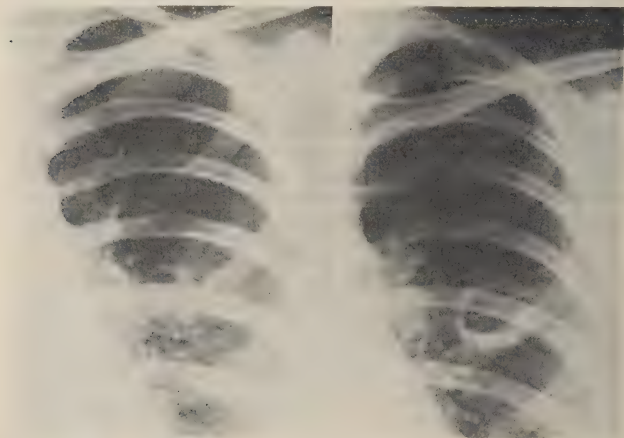


FIG. 2 (Case 2). A (Left). Roentgenogram exhibiting a fine exudative lesion in the second left space anteriorly and behind the third and fourth ribs adjacent to the root.  
B (Right). Roentgenogram taken six weeks later showing a large cavity with a fluid level in the left lung.

100°F. developed, and in another x-ray film a large cavity with a fluid level was recognized in the left lung (fig. 2B). This case is instructive in revealing poor resistance, rapid destruction of the lung; yet despite the cavity with fluid level, bacilli failed to appear in the sputum. Pneumothorax was advised, but patient rejected this recommendation and disappeared from observation.

*Case 3.* I. D. On May 20, 1942 he reported for induction and was rejected on the basis of positive x-ray findings. When I saw him he had no symptoms referable to lung disease. On May 29, 1942 he was x-rayed and showed diffuse infiltration involving the right upper lobe, apex to third rib, with two small areas of highlighting. The diagnosis of tuberculosis

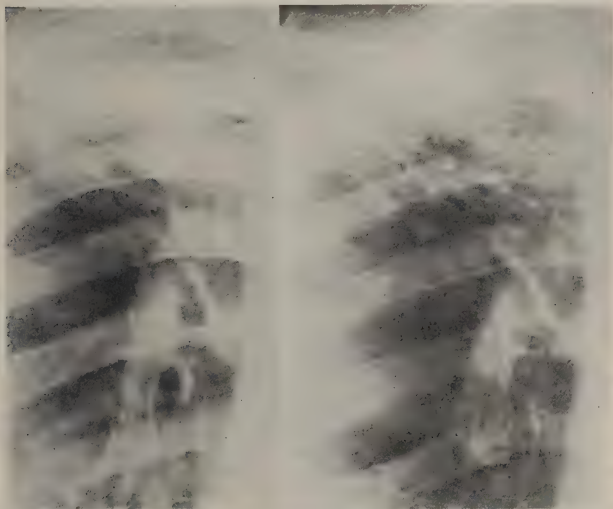


FIG. 3. (Case 4). A (Left). Roentgenogram, taken on September 16, 1943, showing a lesion in the right apex down to the second rib in front.

B (Right). Roentgenogram, taken on July 14, 1944, showing extensive fibrosis, suggesting previous pathological activity.

was made, corroborated by a sputum examination. In June 1942, he received his initial pneumothorax. This has been continued to date. After resting for about six months, he returned to work and has been working since then.

*Case 4.* J. S., a short, stout, heavily built man was rejected by the Draft Board on the basis of x-ray findings shortly before I saw him in July 1943. He had no subjective complaints, and there were no objective findings. X-ray examination disclosed a lesion in the right apex down to the second rib in front. The sedimentation rate was normal, a differential white blood cell count was normal, but the Mantoux tuberculin test was strongly positive. Repeated sputum examinations were negative. He continued to practice his profession of the law, and refused to take any rest. An x-ray made one year later revealed a marked change in the original lesion with the appearance of many linear fibrotic strands. In retrospect it may be stated that the lesion at the right apex was not entirely stabilized,



that he ran a risk by not taking bed rest at least for a short period. It appears that his own resistance was sufficient to overcome whatever handicap was present in the lesion. The subsequent fibrosis within one year's time would corroborate the suspicion that the original lesion was anatomically active, if not clinically so. Despite the character of the lesion, he failed to exhibit any clinical symptoms or objective findings of clinical activity.

*Case 5.* H. M. was first seen in April 1943, after rejection by the Draft Board because of a "spot on the lung." He had no subjective symptoms, and physical examination of the chest was negative. The sedimentation rate was normal. X-ray examination showed a fibrotic deposit in the left first space near the axilla. This deposit was thoroughly circumscribed and of uniform density. Repeated sputum examinations were negative. He was advised to remain under observation but was not put to bed. His last x-ray examination on March 9, 1944, after eleven months of observation, showed little change in the original lesion, suggesting that this was a well arrested primary lesion.

*Case 6.* T. P. was seen by me first in January 1943. From October 1941 to December 1942 he was confined in a City Tuberculosis Institution, where he exhibited widespread disseminated hematogenous disease with a positive sputum. Pneumothorax was attempted on the left side and abandoned owing to adhesions and prompt development of fluid. He observed complete bed rest all during his stay in the hospital. The exudative lesions disappeared, replaced by many fine scars. Evidence of the hematogenous infection is verified by the presence of many fine calcified tubercles. Sputum had been negative prior to discharge from the hospital for many months. Since then, he has been under observation by me and right along has denied subjective complaints. Physical signs throughout this period were negative. Repeated x-ray examinations showed no change in the x-ray findings. In July 1944, after an interval of almost three years of negative sputum, bacilli appeared in the sputum. This examination was followed by two subsequent ones which were likewise positive. The interesting feature in this case is the complete absence of change in the x-ray findings absence of physical signs or subjective complaints. This case illustrates the value of sputum examinations in addition to x-ray studies, and that in this case x-ray examination alone could not have been depended on for a complete evaluation of his condition. Patients who develop arrested disease should remain under observation not only for x-ray studies but also for sputum examinations.

*Case 7.* A. D., one sister died of pulmonary tuberculosis, three brothers are now seriously ill with it. I saw him first in October 1942, three weeks after he was rejected by the Signal Corps on the basis of an x-ray film. When I saw him he had no symptoms referable to his lungs. Repeated sputum examinations were negative. X-ray studies revealed a soft infiltration in the first and second spaces and behind the second rib on the left side near the axilla (fig. 4A); another smaller one, at the left apex immediately above the clavicle. A Mantoux test was 4 plus, erythrocyte sedimentation rate (Cutler method) was 15. He was put to bed, and exercise was begun six months later. His sedimentation rate dropped to 11, and an x-ray study showed fibrosis in the left second space (fig. 4B). In the fall of 1943 he went back to college for a few months, and then took a job at which he has been working full time ever since. His last x-ray film shows a typical linear fibrosis, so often seen as an end result in the exudative lesions of early adult tuberculosis.

*Case 8.* F. F., consulted me in September 1938, complaining of morning nausea, stuffiness in the nose, and a post nasal drip. An x-ray film of the chest which she brought along with her revealed linear fibrosis at the right apex above the clavicle in the first and second intercostal spaces, fan-shaped, radiating from the root (fig. 5A). I advised her to remain under observation. Repeated x-ray examinations showed no change. She was treated by a rhinologist for nasal obstruction. Operation advised by him was refused. Sputum was repeatedly negative. She continued working and gained weight. She was psychoneurotic and complained of many bizarre symptoms not referable to her chest. Patient married in October 1940. In March 1942 an x-ray film showed no change. One year later, in April 1943, she informed me that she went through a pregnancy and that her baby was now three months old. Pregnancy and confinement were normal. In the meantime she developed

hay fever, and skin tests revealed reaction to various pollens and grasses. X-ray examination in May 1943 revealed a slight spread in both lungs (fig. 5B), not accompanied by subjective symptoms or objective findings. The first suggestion of a change in x-ray finding became visible following the birth of her baby. Because this change made exposure of baby to her risky, I advised separation and admission of the mother to a sanatorium. Fibrotic lesions may remain stabilized for years and be upset by an intercurrent episode. In this

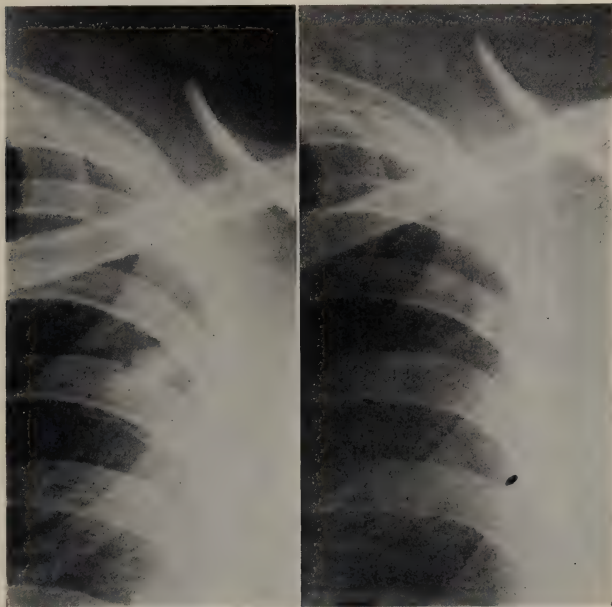


FIG. 4 (Case 7). A (Left). Roentgenogram showing soft infiltration in the first and second spaces and behind the second rib on the left side near the axilla.

B (Right). Roentgenogram taken six months later showing fibrosis in the left second space.

case, strain of pregnancy, confinement and care of her baby may explain the spread. Despite this spread, she gave no complaints and physical examination was negative. The diagnosis in this case rested entirely on the x-ray findings.

*Case 9.* A. M., a nurse, 22 years of age, who was exposed to patients suffering from pulmonary tuberculosis. In November 1937, an x-ray film revealed a soft infiltration in the left second interspace. She was put to bed at once, and artificial pneumothorax instituted. This treatment was maintained for about five years. She made a complete recovery. Diagnosis in this case was made on the basis of a routine x-ray examination (figs. 6A and B). She had no subjective symptoms or physical signs. This case illustrates occupational tuberculosis for which she received full compensation.

*Case 10.* B. L., 22 years old. Father died of tuberculosis. She gave a history of frequent head colds. In July 1942 she was placed in a hospital for observation and there x-ray

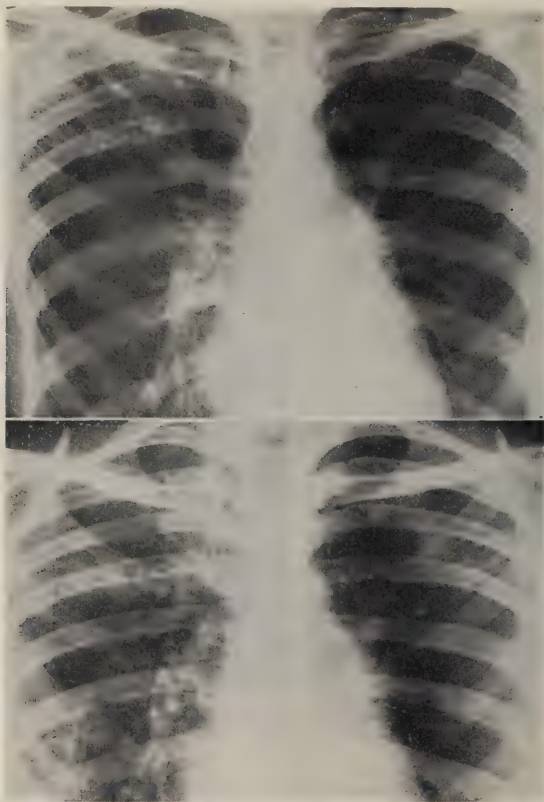


FIG. 5 (Case 8). A (Top). Roentgenogram exhibiting linear fibrosis at the right apex above the clavicle in the first and second intercostal spaces, fan-shaped, radiating from the root.

B (Bottom). Roentgenogram taken five years later showing a slight spread in both lungs.

studies revealed a small soft infiltration at the left apex. Repeated sputum examinations were negative. Physical examination of the chest was negative. I saw these x-ray films and they differed in no way from those I made in January 1944. She was put to bed and

kept at complete rest for about six months. The last x-ray studies made in September 1944 shows almost complete disappearance of the original lesion. A residue of a few fine scars is visible in the last film.

*Case 11.* S. S., consulted me on January 30, 1942, because of nervousness, irritability and general fatigue. She had no pulmonary complaints and there were no physical signs in her chest. The thyroid was slightly enlarged. She had a tremor of the fingers and an increase in the superficial reflexes. X-ray examination of the chest showed a large "dumb-bell" deposit in the left upper lobe (fig. 7A). This lesion looked old, fibrotic and stabilized. Suspicion of hyperthyroidism was entertained and later proven by a basal metabolic rate. She was put to bed because of a moderate hyperthyroidism. Sputum was persistently

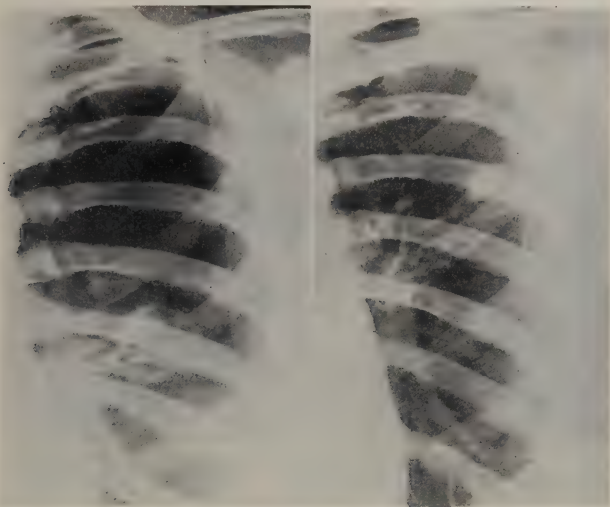


FIG. 6 (Case 9). A (Left). Roentgenogram, taken on April 27, 1943, following a pneumothorax.

B (Right). Roentgenogram, taken on June 14, 1944, following re-expansion.

negative. After resting for several months, she went back to her work. Her post nasal drip was due to suppurative pansinusitis and she was operated for this condition successfully. Later she became pregnant but aborted at the end of the third month. I saw her last in February 1944, when she stated that she was pregnant again, had put on weight and retained it. X-ray examination in January 1944, showed a definite change in the shape and size of the original infiltration (fig. 7B). This would suggest that what we considered stabilized and fibrosed was not entirely so. Further improvement has since occurred and there is a possibility that without treatment the original lesion might have broken down and given rise to clinical symptoms. Indeed, she is not "out of the woods" yet, and was advised to remain under observation.

*Case 12.* Y. D. C., a young girl eighteen years old, whose two brothers and father died of pulmonary tuberculosis. I saw her first in December 1942, after rejection for a position

on the basis of pre-employment x-ray examination which revealed a lesion in the left chest. I saw this film and a lesion was seen above the left clavicle and in the first left interspace. She gave no complaints and the physical examination was negative. A Mantoux tuberculin test was 4 plus but the erythrocyte sedimentation rate (Cutler method) was 6. An x-ray made by me showed a large infiltration in the left first interspace and above the left clavicle. She was put to bed for about six months, and the last x-ray made in October 1943, showed marked improvement in the infiltration which seems to be stabilized. She has since gone back to work and disappeared from observation.

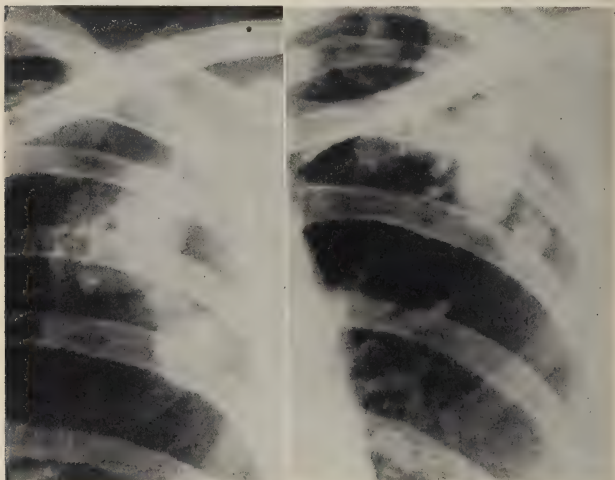


FIG. 7 (Case 11). A (Left). Roentgenogram, taken on January 13, 1943, showing a large "dumbbell" deposit in the left upper lobe.

B (Right). Roentgenogram taken two years later showing a definite change in shape and size of the original infiltration, the isthmus between the two larger lesions disappeared. The lesions have contracted and exhibited more fibrosis and calcification.

#### PRIMARY COMPLEX

This is characterized by the deposit of tubercle bacilli in any part of the lung and simultaneous enlargement of the regional lymph nodes. Allergy as revealed by the skin test (Mantoux) becomes positive in about four to six weeks following the lung invasion. The inflammation in the hilar nodes recedes simultaneously with that in the lung, but progresses when the lesion in the lung does likewise. The primary complex can heal so thoroughly that years later a skin test may prove negative.

The calcified node of Ghon is present in about twenty per cent of all adults. A second primary complex can occur years later, even in the fourth or fifth decades, and repeats the same cycle as the first with fibrosis and calcification in



the lung and hilar nodes. Once the original infection heals, it undergoes no further change in size and this characteristic is pathognomonic and distinguishes it from the secondary or adult type of infection. A Ghon's node remains stationary in size over the years. The primary tubercle may not calcify completely but may undergo fibrosis only, or it may calcify in part and remain partly caseous to become the source of infection (endogenous) at any time. It may show very little lime or only a few fine fibrous linear strands in the midst of a "shower" of lime dust.

The primary complex is benign and attended by a negative sputum, but at times the gavage may be positive, and exceptionally a primary complex can become serious through caseation and bronchogenic spread and assume all the characteristics of severe adult disease.

The primary pulmonary lesion may leave only fine scars such as thickening of the apical cap, thickening of any portion of the pleura, or in inaccessible portions of the lung such as the mediastinal surfaces, the diaphragmatic base, or the posterior sulci. Occasionally one sees a calcified plaque just below the level of the diaphragm in the usual postero-anterior plate indicating the low position of the primary tubercle. The knowledge of the differentiation between the primary and adult type of disease and the characteristic reaction of the allergic pulmonary tissue to the invader evolved gradually. In all these studies, the x-ray has played the leading role.

With the formation of the primary complex, bacilli may leave the hilar glands, find their way by way of the lymph stream into the circulation, enter the right heart and become deposited in the lung itself. Many instances of calcified small discrete nodules at the apices which act so benignly owe their origin to this early infection. This hematogenous route also explains many miliary infections of the lesser circulation which heal and many infections in the kidneys and bones with negative clinical chest x-ray findings.

At times, before the original lesion in the lung heals, tubercle bacilli lodged in a lymph gland involved in the primary infection enter another area of the lung. These secondary lesions either recede or break down as in the adult form of disease (intermediate endogenous superinfection). Adult type cases are observed in whom no outside source of infection could be traced and in whom a fresh infection occurred long after the primary one (endogenous infection). In some cases a generalized miliary infection with or without involvement of the meninges takes place resulting fatally, or if limited to the lesser circulation, recovery not infrequently follows leaving behind the telltale evidence in the x-ray film—the so-called "snowfall appearance." At autopsy, not infrequently, the miliary form of disease can be traced to a caseous node that had never undergone complete healing and that had persisted in this condition for forty or fifty years. Years ago it was believed that adults developed clinical pulmonary tuberculosis only from bacilli within the body (endogenous infection). Later on, definite proof was established that many adults develop tuberculosis not only from bacilli within but also from without the body (exogenous infection).

Young people with a negative skin reaction require no further attention.

Those with a positive reaction, confirming the presence of a primary infection or worse, should always have the benefit of an x-ray examination and this should be repeated periodically. Among adults, especially in large urban communities where the number of reactors is always large, screening can be limited to examination with the x-ray alone.

Clinical tuberculosis, the secondary or adult form, favors the subapical portion or the mid-portion of the lungs. A very small lesion can be overlooked; it must be looked for with the greatest care and diligence. "Soft" films are preferable for this purpose. "Hard" films will over-ray a small soft lesion. A small lesion may be concealed behind a rib or behind the clavicle. Under such circumstances the x-ray taken at a different angle may reveal it. Special stereoscopic apical plates are a great aid in this connection. The important point is to discover it before it has grown to any size, before it has caseated and softened, and before bacilli make their appearance.

Considerable patience, experience, skill and judgment are required to differentiate between x-ray shadows and in the interpretation of their significance. Exact diagnosis is not always possible; considerable time and observation supported by thorough physical examination, complete history and laboratory procedures, may be required before a competent judgment can be established. It should be realized that our knowledge of this field is far from complete. All laboratory facilities, such as gastric lavage, cultures, animal inoculations, and on occasion even bronchoscopic drainage for study of bronchial secretions, must be utilized in order to reach a conclusion. In many of these cases the erythrocyte sedimentation rate, the differential white blood count, the monocyte lymphocyte (Medlar) index may throw no light on the matter. Obviously, the temperature and pulse rate in these cases are always normal, and these patients having no symptoms, have no complaints. The chief reliance at present is placed on the interpretation of the shadows cast by the x-ray and their significance.

In the adult type of tuberculosis, differentiation must be made from lobular pneumonitis, from unresolved or slowly resolving pneumonia, from lobar pneumonia, from lobular atelectasis, infarction, encapsulated effusion, localized bronchiectasis, primary or secondary neoplasm, abscess, foreign body, anatomical malformation of the ribs, callus formation, mycotic infection, and in recent years from atypical pneumonia. In some women the shadow cast by the nipple may be mistaken for an infiltration. Calcified cervical glands just above the clavicle may cast fine apical shadows resembling calcified tubercles inside the lung. Stereoscopic apical plates will assist in the differential diagnosis.

In the preclinical type, almost complete dependence for diagnosis, prognosis and treatment is placed on serial x-ray films. If a lesion does not change after many months, especially if it looks fibrotic, it probably requires no further attention than a checkup with an x-ray every four to six months. It should be kept in mind, however, that a small soft lesion can also remain static for a year or more and then break down rapidly. Such cases are very trying and difficult to interpret and suggest that there is much more to be known about this subject before we can diagnose all such lesions properly and apply the most rational

treatment. A lesion that shows a tendency to grow or to caseate is the one that requires prompt and immediate attention, and to discover one of them is almost synonymous with saving a life. Amberson and Riggins (6) reported a five year study among student nurses at Bellevue Hospital. Of 492 nurses observed, not a single death took place. Such is the advantage of early diagnosis and prompt treatment and in a measure compensates for the greater hazard to which they are exposed by virtue of occupation. Stiehm (7) reported that in fourteen years at Wisconsin University, an average of ten tuberculosis cases were found annually, but with the introduction of case finding by x-ray, during the first year of its application as a routine measure, the number of tuberculosis cases rose to 43, a rise of 330 per cent over the ten year average. P. K. Telford (8) states that "a large number of minimal cases remain minimal and many of them do so in spite of violation of the standard rules of treatment." J. A. Miller (9) says "in the great majority of cases these lesions are latent and innocuous and will always remain so under ordinary conditions of life." It is important, after finding these minimal lesions, to differentiate between the primary and secondary lesions, between the potentially active and inactive, treat the active lesions promptly and fully, leave the inactive lesions alone and keep the doubtful lesions under observation with serial x-ray studies for one or more years if necessary before final disposition is made and before a final prognosis is pronounced. One is sorely perplexed when a positive sputum appears in a case in which the nodules appear thoroughly calcified with no evidence of fresh exudation or infiltration and with no evidence of endobronchial tuberculosis. In such cases it is hazardous to render a complete opinion on a single film and at a single examination.

I have had several experiences in which nodular cases, apparently thoroughly arrested, shed a few bacilli intermittently and finally ceased altogether. If bacilli persist, a tomogram may disclose a tiny cavity. If this is negative, bronchoscopy is indicated to exclude endo-bronchial tuberculosis. A peribronchial tubercular gland may discharge some of its contents into the lumen of a bronchus.

Since a large number of young people now reach adulthood insensitive to tuberculin, a primary infection occurring in them may not behave as it does in childhood; it may not heal so readily. Instead, it may progress rapidly to the adult type of disease, break down with cavity formation and progress alarmingly. Particularly is this possible in young girls coming from rural areas, many of whom are insensitive to tuberculin, who enter a nurses' training school and work in a hospital where they come in close contact with many open cases of advanced tuberculosis. Under the conditions governing their employment, they are necessarily exposed frequently to repeated and large doses of bacilli. On the other hand, a tuberculin positive case shows more resistance to exogenous infection, and when infection does occur the response to it is the one we are accustomed to associate with the adult type of tuberculosis.

A primary infection occurring in an adult must be differentiated from a secondary infection. When a person is known to have had a negative skin test

and develops a small pulmonary lesion, one is justified in calling it a primary lesion if with it there is associated a typical reaction in the hilar glands. The important thing to remember is that most primary infections resolve without any treatment and leave behind as evidence of its former existence—the infection of Ghon and calcified hilar glands. It would be erroneous to institutionalize such persons and deprive them of their earning power, besides injuring their morale, and in view of the prejudice still prevalent in the community in regard to tuberculosis, injure their opportunities for obtaining future employment.

It must be borne in mind that a secondary infection produces practically no change in the hilar lymph nodes. For this reason, in all hospital personnel at least, not only is it advisable to have routine x-ray films repeated semiannually but also routine preemployment tuberculin tests so as to distinguish the sensitive from the insensitive cases. This will assist in differentiating primary from secondary lesions. Tubercle bacilli falling on virgin soil produce a different reaction than on an allergic soil; moreover, the treatment and the prognosis are far different in the two categories.

#### TREATMENT

The treatment of the “early” case diagnosed by x-ray findings alone is eminently satisfactory. There are no symptoms to treat since there are none present. Physical signs, of course, are absent. All laboratory tests may prove negative. A positive sputum vitiates a diagnosis of “early” disease since it indicates a breakdown or ulceration of tissue and places the case in a different category which may demand the additional assistance of artificial pneumothorax. In the typical case, bed rest will hasten absorption of the exudate with replacement fibrosis in about six to nine months. The fibrosis tends to become linear and not circular as in a primary infection. Rehabilitation may be commenced after this period with the hope of returning the patient, preferably back to his former occupation.

If the initial x-ray film reveals beginning cavity formation but a negative sputum after a thorough search, bed rest alone still remains the treatment of choice. In the event that the sputum turns positive, pneumothorax is indicated. On the other hand, in the presence of a spread of the original lesion or an increase in the size of the cavity, even in the absence of a positive sputum, pneumothorax is likewise indicated. In this connection the greatest care must be exercised not to confuse a tubercular cavity with an ordinary abscess even though small. Usually a tubercular cavity is associated with a positive sputum. In a very small cavity or before the cavity is established, difficulty in finding bacilli may be encountered and one may have to go to great lengths in the search for them from gavage, to culture, animal inoculation, and even bronchoscopic aspiration.

X-ray studies are indispensable in evaluating the results of treatment, establishing criteria for the choice of a particular form of treatment or possible change in treatment and for prognosis. After arrest of the disease has been attained, periodic x-ray examination are indicated for the ensuing several years as a form of insurance, for recurrence is always possible.

The cost of treating the early case is small by comparison with the more advanced form which may require an added pneumothorax or some type of more drastic surgery. In the latter, disability may extend over a period of months or years.

The cost of the investment rises with the advancing stage of disease, and the anticipated dividend return varies inversely with the stage. From the viewpoint of community interest, failure to discover the early case represents an avoidable heavy burden on everyone. To the individual victim it may represent the difference between normal living, with economic independence and self respect, to more or less chronic invalidism and dependence with ultimate termination in an untimely end.

The task implied in the solution of the difficult problem confronting us is beyond the capacity of any single physician, patient or group, and its solution resides in the voluntary acceptance of responsibility by an intelligent collective, social consciousness.

The stabilized symptomless lesion, be it remembered, does not always remain as innocent as it looks. It may remain so for years, but under provocation, change its tempo.

The preclinical lesion deserves treatment promptly. Delay, even of a few weeks, may convert a favorable into an unfavorable outlook. Those who cannot provide treatment for themselves should be institutionalized without delay and not be obliged to remain on a waiting list. To refuse admission promptly to such a patient may prove in the end an invitation to disaster. Beds must at all times be available to those, who, out of necessity, must have them.

#### PREVENTORIUM FOR TREATMENT OF PRECLINICAL PULMONARY TUBERCULOSIS

In the past, preventoria for children received considerable attention. In its day and in its way, considerable benefit was derived through these institutions. Children who were below par physically and those who came from a tuberculous milieu were admitted to them, and the physical and educational benefits provided by them justified their existence. With the knowledge that clinical pulmonary tuberculosis is uncommon in older children, interest in them began to lag.

Now the time has come when the idea of the preventorium can be expanded and put to a more constructive use than ever before. May I here enter a plea for a practical use of the preventorium? It can be used for the care of pre-clinical cases with the hope of preventing clinical disease. This is a true function of a preventorium, as its name implies, to treat the disease before it manifests clinical symptoms. A sharp distinction must be drawn between this type of ease and the one that presents a positive sputum. The latter should never be admitted to a preventorium. This type institution should under no circumstances house a positive sputum; likewise, when a patient in it develops a positive sputum, transfer to a sanatorium should be effected immediately. A sharp distinction must be drawn between the preventorium and the sanatorium. The sanatorium is qualified to employ more advanced technical methods in a more



advanced type of disease. In this manner all positive cases could be segregated from the negative ones. Moreover, the cost of care in the preventorium would be minimal since treatment would be simple and consist mainly of bed rest alone. The size of the medical, nursing staff and general personnel could be held down to a minimum. Laboratory facilities could be few and inexpensive; the one essential requirement would be an efficient x-ray outfit. Psychologically, the trauma to the individual would be minimal for he would know that his outlook for complete recovery is ideal, that he is not contagious to others; he would be free from the social stigma which still prevails currently, his chances for future employment would be better, and in young girls the outlook for marriage would not be retarded.

#### SUMMARY

(1) The x-ray has brought more progress than any other discovery in the history of tuberculosis. It is the one indispensable instrument and has relegated the stethoscope to a position of subsidiary importance.

(2) The preclinical case is made evident by the x-ray only. The preclinical case presents neither signs nor symptoms; since he has no reason to go to the doctor, the doctor must go to him.

(3) The number of cures of preclinical cases can rise to staggering figures.

(4) The number of reactors has steadily diminished in recent years. This is not an unmixed blessing. A first infection in a non-sensitized young adult, under certain circumstances, can lead to serious consequences. Among pupil nurses, tubercular lesions are more frequent in young non-sensitized individuals when exposed to open tuberculosis than the positive reactors.

(5) Tuberculosis in many states of the Union has been made a compensable disease.

(6) All young people between the ages of 16 and 30 should be x-rayed annually, regardless of social, occupational or financial status. Those with suspicious lesions should be kept under close observation.

(7) Preventoria should be established for the treatment of preclinical cases. The preventorium is an ideal institution for this purpose, to prevent progression of the preclinical to the clinical stage of disease; the preventorium should under no circumstances house a positive sputum case.

Establishment of the preventorium would complete the triad of institutions for the tuberculous. (a) The *preventorium* to treat the preclinical-negative sputum-stage of the disease. (b) The *sanatorium* for the positive sputum case, requiring possibly pneumothorax or other adjuvant procedure, such as pneumolysis. (c) The *hospital* for cases of advanced disease requiring thoracoplasty or other advanced type of chest or general surgery or of other technical procedures, or of specialists in branches of internal medicine, as diabetes, heart disease, chronic nephritis, etc., and of a well equipped laboratory which is more properly the possession of a large hospital in the city, than of a sanatorium located at a distance.

## REFERENCES

- (1) EDWARDS, HERBERT: Supp. Vol., Am. Rev. Tuberc., 1940.
- (2) Am. J. Nursing, 40: 10, 1940.
- (3) HEIMBECK, J.: Tubercle, 18: 97, 1936.
- (4) HEIMBECK, J.: Über Infektion und Wakzination bei Tuberkulose, Med. Klin., 29: 1731, 1933.
- (5) BRAHDY, LEOPOLD: J. A. M. A., 114: 102, 1940.
- (6) AMBERSON AND RIGGINS: Ann. Int. Med., 10: 156, 1936.
- (7) STIEHM, R. H.: Am. Rev. Tuberc., 32: 171, 1935.
- (8) TELFORD, P. K.: Am. Rev. Tuberc., 37: 57, 1938.
- (9) MILLER, J. A.: J. A. M. A., 111: 111, 1938.

## THE PREOPERATIVE AND POSTOPERATIVE CARE OF THE DIABETIC PATIENT REQUIRING SURGERY

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The diabetic patient requiring surgical intervention presents, in the main, the following problems:—

- (1) The prevention of ketosis and coma.
- (2) Good clean healing of the operative area.
- (3) Is a glycosuria harmful?
- (4) The prevention of insulin shock.

Because of the availability of insulin, their solution should not be difficult. However, because of the tradition that glycosuria is harmful, the surgeon still approaches the diabetic patient with very much concern. Furthermore, this somewhat fearful approach is also due to the fact, that most of the subject matter on the preoperative and postoperative care of the diabetic patient, has dealt with general principles rather than specific details of management thus failing to place exact procedures into sharp focus.

It is, therefore, the purpose of this paper not only to reiterate the fundamentals, but also to present the details explicitly, for the preoperative and postoperative care of the diabetic needing surgical procedures. In addition I shall discuss, briefly, the question of glycosuria and wound healing as many believe that the two are intimately related.

*Principles.* 1. *The prevention of ketosis and coma.* This can best be accomplished by adequate doses of insulin and glucose.

2. *The prevention of dehydration and loss of base.* As a general rule in surgery the maintenance of the water balance of the body has gained wide acceptance. This is even more important in the diabetic because of his tendency to lose base and fluid when he develops an actual or relative insulin insufficiency. Such a want may occur under the following circumstances:—

- (a) Willful omission of insulin.
- (b) The development of infections.
- (c) Such complications as, hyperthyroidism, acromegaly, Cushing's syndrome, and adrenal tumor (pheochromocytoma).

I want to emphasize that such insulin insufficiency is not merely synonymous with a glycosuria. There is a difference. Patients whose insulin doses are inadequate will experience frequency, polyuria and dehydration. They will lose weight, and often reveal an acetonuria. On the other hand, the patient whose insulin needs are met amply, may and even does excrete sugar—often in considerable quantity—yet, he will not experience frequency, thirst, nor polyuria and his weight will not fall. It is obvious, then, that adequate doses of insulin are *most* important, and as a safety valve against loss of base the administration of salt is very useful.

*Procedure.* A. Elective Surgery.

(1) The day before the operation the patient is given 1.0 gram (15 grs.) of salt every two hours. This is followed by a glass of water (200–250 cc.). The salt may be administered in capsules or tablets.

(2) The patient is given his usual ambulatory diet as well as his usual quantity of insulin.

(3) The urine is tested for sugar and acetone either at each voiding or group urines may be examined. The usual routine groupings are from 7 to 11 A.M., 11 A.M. to 4 P.M., 4 to 9 P.M., and 9 P.M. to 7 A.M. The result of the examination may reveal (a) a sugar free urine, (b) a glycosuria of variable concentrations, (c) a glycosuria and a ketonuria. It is obvious that the first possibility requires no therapy. The occurrence of a glycosuria *only*, without any of the symptoms of diabetes or acetone, also may go untreated. However, a glycosuria with a ketonuria demands energetic treatment and the use of regular insulin is imperative. The quantity prescribed is governed by the glycosuria. For a four plus specimen (yellow-red) 20 to 25 units are given; for a two to three plus specimen (green with yellow sediment) 15 units, and if following this routine the subsequent specimens are sugar free 200 cc. of orange juice are given. This technique is to be continued as long as ketone bodies are detected in the urine. Usually, the ketone bodies will disappear rather rapidly and the administration of orange juice will protect the patient from insulin reactions. As a result of this technique the patient will be well hydrated as both the salt and glycogen deposits will bind water.

Since in the diabetic patient insulin is such an efficient agent for the utilization of carbohydrates—namely their oxidation and their storage as glycogen, I have used it not infrequently for increasing the glycogen reserves in the preoperative patient. This was done whether the urine was sugar free or revealed a four plus glycosuria. The technique is simple. The day prior to the operation the patient is given 15 units of regular insulin every three hours and this is followed by 200–250 cc. of orange juice. Whenever this routine was followed there was usually a three to four plus glycosuria at each voiding but no ketonuria. This procedure is used in conjunction with the usual routine of the patient's diet and insulin dosage, and *not* in place of it. No pre-operative blood sugars were done.

(4) The question of anaesthesia is governed by the general situation rather than the diabetes *per se*. Prudence, however, dictates the avoidance of the hepatotoxic anaesthetics. Ether, nitrous oxide, cyclopropane or any local anaesthetic may be employed.

(5) During the operation the patient receives an infusion of 1000 cc. saline and 5 per cent glucose to which are added 25 units of insulin. This is given slowly. In patients past sixty or those younger in whom there is evidence of myocardial weakness, because of vascular or rheumatic disease, the above solution is to be given by hypodermoclysis. If the operator prefers to use the intravenous route, it is important to observe the venous pressure so as not to overload the right heart.

(6) When the operation is over, a retention catheter is introduced into the urethra and either clamped or attached to a receptacle at the bed side.

(7) Specimens are then taken every two to three hours and tested for sugar and acetone. No treatment is instituted if only a one or two plus glycosuria is found. If the specimen shows a four plus concentration, 15 units of regular insulin are given. This may appear as a low dose, but it is safer as it will aid the glycogen deposition, but is not large enough to induce hypoglycemia. If, however, both sugar and acetone are present then the routine outlined above is employed. Briefly, this calls for 20 units regular insulin for a 4 plus specimen and 15 units for a three plus specimen. The specimen should be taken every two to three hours and orange juice should be given as soon as the ketone bodies vanish even though the specimen still has a one to two plus glycosuria. If the patient is unable to take fluids by mouth he should receive fluids by hypodermoclysis—5 per cent glucose in saline 1000 cc.

(8) After a 24 to 36 hour period the catheter is removed and the urine is examined at each voiding. The treatment follows the above pattern. In case the patient cannot void he should be catheterized and if acetone reappears he should be treated as energetically as directed in the section above.

(9) In most cases the patient will be permitted to have fluids by mouth 48 hours or even sooner after the operation. In certain gastrointestinal procedures it may be desirable to withhold solid food for longer periods or forbid anything by mouth, the patient's fluid balance is maintained by clysis 2000 to 3000 cc. daily of 5 per cent glucose in saline and each infusion is covered with 20 to 25 units of regular insulin. Care must be exercised at all times not to overload the right heart by giving the fluid too rapidly or too much at one time.

When the immediate emergency is over and the patient is permitted food, he is allowed about one-half to three-quarters of his preoperative diet and sufficient protamine insulin to keep him free from the symptoms of diabetes as well as free from ketonuria.

For example, if the patient's preoperative diet was approximately protein 70 gm., fat 70 gm., and carbohydrate 250 gm., and he managed to be free from any and all symptoms of diabetes with 30 units of protamine insulin though showing a glycosuria, his postoperative diet may begin with protein 50 gm., fat 50 gm., and carbohydrate 150 gm., as well as 20 units of protamine insulin. Both of these components are gradually increased as his appetite improves, until our criteria for satisfactory control have been attained. These have been reported in detail elsewhere (1).

*B. Emergency Surgery.* No diabetic, irrespective of the severity of the diabetes should be denied emergency surgical procedures. Furthermore, no operation need be delayed. This should be axiomatic. To insure the welfare of such patients it is important more than at any time, to aim for rich glycogen stores in the liver. This view point is now well accepted, having been emphasized by McKittrick and Root in 1940 (2) and reiterated by Root in 1942 (3). To attain this aim the patient is given an infusion of 5 per cent glucose in 1000 cc. of saline to which 25 units of insulin have been added, or the insulin may be given at the beginning of the infusion, subcutaneously. This is repeated immediately after the operation. A retention catheter is then introduced and the directions



given above are followed. It will be seen that at no time during the treatment, an effort was made to maintain the urine free from sugar. As a matter of record it will be noted that as soon as a specimen was sugar free, orange juice was given. This not only served as a buffer against an insulin reaction, but also made glucose available in the blood stream, thus creating a situation which was conducive to glycogen deposition, namely—glucose and insulin. Because of this effort to maintain an intermittent or continuous hyperglycemia and the resulting glycosuria the question may be posed justly as to what extent such a hyperglycemia influenced the healing of the operative area. This was observed, and the following cases are illustrative of the results as well as the technique followed.

*Case 1.* A 56 year old female was admitted for a breast amputation. She had a mild diabetes for 8 years. She took no insulin. She was operated June 8, 1940 and on the morning of operation she was given 1,000 cc. 5 per cent glucose in saline by vein, and 25 units of regular insulin. Another similar infusion of 1500 cc. and 25 units of insulin were given in the afternoon. A catheterized specimen late that evening revealed a 4 plus glycosuria and 20 of regular insulin were given.

| <i>Date</i> | <i>Time</i> | <i>Qualitative Reaction</i> | <i>Treatment</i>         |
|-------------|-------------|-----------------------------|--------------------------|
| 6/ 9/40     | 2:00 A.M.   | 4 plus                      | 20 units regular insulin |
|             | 10:00 A.M.  | 3 plus                      | 15 " " "                 |
|             | 4:00 P.M.   | 2 plus                      | 10 " " "                 |
|             | 7:30 P.M.   | 0                           | 200 cc. orange juice     |
| 6/10/40     | 4:00 P.M.   | 0                           | 200 cc. orange juice     |
|             | 8:00 A.M.   | 2 plus                      | 10 units regular insulin |
|             | 12:15 P.M.  | 4 plus                      | 20 units regular insulin |
|             | 3:00 P.M.   | 4 plus                      | 20 units regular insulin |
|             | 6:30 P.M.   | 2 plus                      | 10 units regular insulin |

No acetone was present in any of the specimens. The patient selected her own food which consisted of small quantities of fruit juices, cereals, eggs, toast, tea, coffee and milk.

On June 11, 1940, three days postoperative she was given a diet of protein 75 gm., fat 75 gm., carbohydrate 200 and 30 units of protamine insulin. From this time on, the specimens were grouped and examined, but *were not* covered with regular insulin even though a glycosuria was present. Of the 25 urine examinations during the following nine days, 19 showed a four plus reaction for sugar; 4 showed a three plus, and 2 showed a one plus. On the 12th day after the operation there was a slough in the thinnest portion of the flap. It was about 1.5 by 1.0 cm. From this area serosanguinous fluid was aspirated. There was no evidence of infection. The patient was up and about. The final result was satisfactory.

*Comment.* It is reasonable to state that this patient had a hyperglycemia during her entire postoperative period and her wound showed no evidence of infection or poorer healing than in other instances of radical mastectomy.

*Case 2.* Patient is a 35 year old female, who had diabetes for over ten years. Her diabetes was moderately severe and it was difficult to control her at all times with 50 to 60 units of regular insulin. This was the situation before the introduction of protamine insulin. She was then treated with protamine insulin 40 to 50 units, and though she revealed a glycosuria during the day, she was symptom free and maintained her weight, showing a gain at times. There was no period of her diabetic life during which she was sugar free even for short intervals. She was admitted to the hospital for a myomectomy.

The day prior to the operation the patient was given 1.0 gm. of salt every two hours. This was taken with a glass of water. Ether anaesthesia was used and at the end of the operation a retention catheter was introduced. She was operated on June 7, 1941. For the following two days specimens were taken every two hours and insulin given as indicated. On the third postoperative day the catheter was removed and she was then given a diet of P60 F60 C150, as well as 25 units of protamine insulin. The following table reveals the quantity of glucose excreted during the next eight days.

| Date    | Glucose in the urine in<br>grams per 24 hours |
|---------|---|
| 6/10/41 | 61.0  |
| 6/11/41 | 131.0   |
| 6/12/41 | 128.0   |
| 6/13/41 | 114.0   |
| 6/14/41 | 138.0   |
| 6/15/41 | 71.0  |
| 6/16/41 | 117.0   |
| 6/17/41 | 100.0   |

The patient's wound healed nicely in spite of this glycosuria. On discharge both the diet and insulin were increased. I have been following the patient since then at monthly intervals and although she continues to reveal a glycosuria she is symptom free and has gained weight.

*Comment.* It is apparent in this case that the postoperative glycosuria did not affect the healing adversely. There were no evidences of infection and healing took place by primary union.

*Case 3.* Patient is a 37 year old female who has had a moderately severe diabetes for the past 5 years. She managed her own case by taking from 32 to 33 units of protamine insulin and eating anything she wished, concentrated sweets included. She was admitted for a uterine suspension and appendectomy. The detailed procedures are best illustrated in the following table.

1. 7/12/43, 1.0 gm. of salt at 10:00 A.M., 2:00, 4:00, 6:00, 8:00 and 10:00 P.M. each dose was taken with a glass of water.
2. 7/13/43, operation under general anaesthesia at the end of which a retention catheter was inserted and clamped. The specimens were then examined and treatment applied as shown below.

| <i>Time</i>    | <i>Qualitative<br/>Sugar</i> | <i>Acetone</i>       | <i>Treatment</i>         |          |         |   |
|----------------|------------------------------|----------------------|--------------------------|----------|---------|---|
| 1:30 P.M.      | 4 plus                       | 2 plus               | Insulin                  | 25 units | regular |   |
| 3:15 P.M.      | 4 plus                       | 3 plus               | "                        | "        | "       | " |
| 5:30 P.M.      | 4 plus                       | 2 plus               | "                        | "        | "       | " |
| 7:30 P.M.      | 2 plus                       | 0                    | "                        | 10       | "       | " |
| 9:15 P.M.      | 4 plus                       | 0                    | "                        | 20       | "       | " |
| <i>7/14/44</i> |                              |                      |                          |          |         |   |
| 1:15 A.M.      | 0 minus                      | 0 minus              | 200 cc. orange juice     |          |         |   |
| 3:15 A.M.      | 0                            | 0                    | "                        |          |         |   |
| 5:15 A.M.      | 0                            | 0                    | "                        |          |         |   |
| 7:15 A.M.      |                              | No specimen examined |                          |          |         |   |
| 9:15 A.M.      | 0                            | 0                    | 200 cc. orange juice     |          |         |   |
| 11:30 A.M.     | 3 plus                       | tr.*                 | Insulin 15 units regular |          |         |   |
| 1:15 P.M.      | 4 plus                       | 1 plus*              | Insulin 20 units regular |          |         |   |
| 3:15 P.M.      | 2 plus                       | 0                    | "                        | 10       | "       | " |
| 5:30 P.M.      | 0                            | 0                    | 200 cc. orange juice     |          |         |   |

\* Patient was receiving salicylates and this may have been a false reaction.

| Date    | Vol. Urine | Sugar<br>Qualitative | Quantitative<br>gms./24 hrs. | Insulin      |
|---------|------------|----------------------|------------------------------|--------------|
| 7/15/43 | 1445       | 4 plus               | 30.2                         | Protamine 35 |
| 7/16/43 | 735        | 3 plus               | 8.7                          | " "          |
| 7/17/43 | 1750       | 4 plus               | 62.5                         | " "          |
| 7/18/43 | 1775       | 4 plus               | 88.7                         | " "          |
| 7/19/43 | 625        | 4 plus               | 26.0                         | " "          |
| 7/20/43 | 900        | 4 plus               | 37.5                         | " "          |
| 7/21/43 | 1400       | 4 plus               | 28.0                         | " "          |
| 7/22/43 | 1315       | 3 plus               | 20.0                         | " "          |
| 7/23/43 | 1250       | 2 plus               | not done                     | " "          |

The patient was discharged on the 13th postoperative day. Her wound healed without any complications. Since her discharge from the hospital she has been taking 35 units of protamine insulin daily. She has not been too careful with her diet. On follow up visits she has always shown a 4 plus glycosuria—a casual specimen. However, she has been free from symptoms of diabetes and ketosis. Furthermore she has maintained, and at times shown a gain in weight.

*Comment.* The postoperative glycosuria did not retard the healing of the patient's wound.

#### DISCUSSION

The above examples demonstrate clearly that a postoperative glycosuria did not retard the healing of the wound, and as there were no evidences of infection, the obvious deduction is that it was not conducive to infection. In the second patient the glycosuria was of considerable degree yet her wound healed by primary union and her hospital stay was not prolonged. Since these facts contradict the prevailing concepts, a review of the available data is desirable, to determine the basis as well as the validity of such existing view points. At the outset it must be stated that a *glycosuria which lacks the protection of insulin is deleterious*. This is a fact that has been borne out by years of experience. However, glycosuria *per se* in the insulin treated patient—particularly protamine insulin—is not harmful. This has been shown in the treatment of both our medical (4) and surgical diabetic patients. It is far from my intention to condemn efforts to maintain the urine free from sugar at all times postoperatively. My contention is that it is unnecessary, and it also involves the element of risk—a hypoglycemic reaction.

The view points concerning the etiology, pathological physiology and treatment of diabetes mellitus and its complications have been changing constantly. In this evolutionary period many beliefs and theories have been replaced by others, which for scientific reasons proved more tenable. However, tradition takes deep roots even in scientific medicine and some beliefs still prevail though they are inferential. Hypotheses have been repeated so often by moulders of medical public opinion, that they have been accepted as facts, without too much inquiry or challenge.

From the very discovery of diabetes, glycosuria was considered deleterious, not only because of its immediate concomitants such as dehydration and base loss, but also as a contributing factor directly or indirectly to complications such as susceptibility to infections, atherosclerosis, retinal changes, cataract

formation and others. This postulate arose in the preinsulin era when the diabetic patient was malnourished, dehydrated, desiccated and it was never clearly defined whether the complications mentioned were due to the glycosuria or the malnutrition. True, both were so closely bound up in the diabetic picture that a clear definition was difficult. But it seems, that it was not even looked for as everyone accepted the situation as axiomatic. There was evidence in the literature that hyperglycemia *per se* was not a contributory factor to infections. In 1911 Handsman (5) found that blood glucose concentration up to 1000 mg. per cent was neither a better medium for staphylococci nor was blood less bactericidal against staphylococci than normal blood. This was telling experimental evidence, which clearly contradicted a reiterated assumption, yet no one accepted this demonstrable fact seriously and the prepossessed idea that glycosuria was conducive to infection, was perpetuated in publications, text books and by word of mouth. Handsman's conclusions were confirmed by others (6). With the discovery of insulin the hypothesis that glycosuria was harmful gained ground. The diabetic patient thrived so beautifully on insulin that all the excellent results were at once attributed to the better control of the glycosuria. Little was said about the patient's nutritive state, for many patients improved their physical status even though they revealed a glycosuria during a good part of the 24 hour period. Could it not be stated, and with justification, that the decrease in complications were due to the patient's gain in weight and hydration, since he was not free from glycosuria? In other words, was it not his gain in weight and better nutritive status which made him less susceptible to infection? Such a view was not entertained, and glycosuria as a harmful actor dominated the field.

In 1936 with the introduction of protamine insulin my associates and I showed by carefully controlled observations that even very severe diabetics can maintain their weight, and be free from the symptoms of diabetes, even though on certain days they excreted as much as 100 gm. of glucose in 24 hours. In the presence of such glucose loss they were in positive nitrogen balance and were remarkably free from localized or general infections during the six week period of observation on the metabolism ward. They were well nourished and not dehydrated. This work was extended to the ambulatory cases and we observed that as long as our patients were well nourished and free from symptoms of diabetes they had no more, nor more severe infections than other patients, even though they always revealed a 4 plus qualitative glycosuria when reporting for their visits. These were patients treated with protamine insulin. Naturally, after a prolonged period of observation we felt that glycosuria *per se* in protamine treated patients is not as harmful as the impression carried over from the perinsulin era attributed to it.

There is no cause for the surgeon to fear glycosuria in the insulin treated patients. Both clinical and experimental evidence support this thesis. Diabetic patients underwent a variety of major procedures and made uneventful recoveries even though they revealed considerable sugar in the urine post-operatively. Green and his associates (7) studied the relation of the incidence

of delayed healing of clean and infected wounds to the height of the blood sugar and degree of glycosuria in 324 patients with diabetes, and found no relationship between the height of the blood sugar and degree of glycosuria, to the healing or infection in clean wounds. This is an impressive number of patients and their report is convincing. These authors did state, however, that "delayed healing of wounds occurs approximately 4 per cent more frequently among diabetics than among nondiabetics of the same age and sex." This is certainly a very small figure and though considered significant it should not influence our attitude toward the diabetic patient requiring surgery.

#### SUMMARY AND CONCLUSIONS

(1) The problems confronting the surgeon who must operate on the diabetic patient were presented.

(2) The principles involved and detailed therapeutic measures were described.

(3) The relationship of glycosuria to wound healing was discussed. Personally treated cases and experimental data were presented as well as clinical and experimental evidence from the literature to show that glycosuria in insulin treated cases was not deleterious, and that wounds healed by primary union in its presence.

(4) The obvious conclusions are:—(a) That no diabetic need be denied surgery; (b) Surgical procedures need not be delayed because of diabetes; (c) That postoperative glycosuria does not inhibit wound healing, nor is it conducive to infections.

#### BIBLIOGRAPHY

- (1) TOLSTOI, EDWARD: Newer Concepts in the treatment of diabetes mellitus with protamine insulin. *Am. J. Digest. Dis. & Nutrition*, 10: 247, 1943.
- (2) MCKITTRICK, LELAND S., AND ROOT, HOWARD F.: Preoperative and postoperative treatment of the patient with diabetes. *Arch. Surg.*, 40: 1057, 1940.
- (3) ROOT, HOWARD F.: Medical aspects of diabetic surgery, *New York State J. Med.*, 42: 2296, 1942.
- (4) TOLSTOI, EDWARD, AND WEBER, FREDERICK C. JR.: Protamine insulin: A Clinical study. *Arch. Int. Med.*, 66: 670, 1940.
- TOLSTOI, EDWARD, ALMY, THOMAS P., AND TOSCANO, VINCENT: Treatment of diabetes mellitus with protamine insulin: Is a persistent glycosuria harmful? Metabolic study of severe case. *Ann. Int. Med.*, 16: 893, 1942.
- (5) HANDSMAN, E.: Ueber die Ursache der Verminderten Resistenz des Diabetickers gegen Infektionen. *Deutsches Arch. f. klin. Med.*, 102: 1, 1911.
- (6) HIRSCH-KAUFMANN, H., AND HEIMAN-TROSIEN, A.: Bakterien Wachstum auf dem Blut Diabetischer Kinder. *Klin. Wehnschr.*, 5: 1922, 1926.
- MARBLE, A., WHITE, H. J., AND FERNWALD, A. J.: The Nature of the Lowered Resistance to Infection in Diabetes Mellitus. *J. Clin. Investigation*, 17: 423, 1938.
- (7) GREEN, JAMES A., SWANSON, L. W., AND JACOBS, CARL A.: Control of diabetes mellitus. *J. A. M. A.*, 115: 518, 1940.



# PSYCHOSOMATIC DISORDERS OF THE GASTRO-INTESTINAL TRACT<sup>1</sup>

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Psychosomatic disturbances of gastro-intestinal function occur in healthy people subjected to unusual emotional stress; they are among the commonest manifestations of emotional stress in neurotic people. Of 269 neurotic patients encountered in a medical out-patient department Friess and Nelson (1) found that 41.5 per cent mentioned gastro-intestinal symptoms as their chief complaint. The abdomen is, indeed, the sounding board of the emotions.

It is the special point of this paper that psychosomatic techniques of diagnosis and treatment must become an integral part of the practice of medicine in order to fulfill their promise and meet the challenge of present day medical problems. The enormous number of psychoneurotic and psychosomatic problems turned up by the Selective Service process and encountered in military medicine indicates where the emphasis must be placed in the future practice of medicine. It is my belief that just as the last World War established psychiatry on a firm scientific basis so will World War II see the final integration of psychiatry into medicine, in other words, psychosomatic medicine.

Just as in a consideration of somatic disease it is necessary to make a definitive diagnosis before we can hope to apply scientific treatment so in psychological medicine it is equally necessary. Hence just as in general medical teaching we have always emphasized the etiologic, anatomic and functional diagnosis so in psychological medicine, as pointed out by Levine (2), it is necessary to make a clinical, dynamic and genetic diagnosis before one can stand on safe ground in regard to psychotherapy. In this connection I would emphasize that psychosomatic medicine does not mean to study the soma less but only means to study the psyche more. Clinical material will be cited to illustrate this point of view.

## THE ORGANIC TRADITION IN MEDICINE

It is highly necessary to speak of the present practice of general medicine in this regard. It seems extraordinary that so little progress has been made in overcoming the organic tradition in medicine. This applies especially to the gastro-intestinal tract which, above all other systems, reflects emotional disturbances. As Alvarez recently stated in an interesting book entitled, *Nervousness, Indigestion and Pain*: (3) "Every gastroenterologist who hopes to be worthy of the name and would like to keep from making one serious blunder after another should be learning all he can about the psychiatry of the apparently sane.

<sup>1</sup> Part of a paper read before the Second Brief Psychotherapy Council, Chicago Institute for Psychoanalysis, Jan. 15, 1944 and presented at the Army Air Forces Medical Meeting, Mitchell Field, New York, February 28-29, 1944.

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Like me, he may not have wanted to get into this field of medicine, but he cannot stay out of it and be a safe internist."

Since we are speaking of the gastro-intestinal disorders it is pertinent to add that vitamins are the order of the day. Not only are vitamins administered in the relatively few conditions for which it has been proved that they are specifically indicated but in addition every obscure illness, physical or psychological, gets its complement of vitamins. The eagerness of the profession to find a physical answer to all medical problems and the gullibility of the public, which also wants to swallow a magic pill to abolish any and all ills, find a common answer in vitamins. The *vita* half of the term is not without significance in this connection. Drug houses and department stores, candy stores and slot machines, peddle vitamins to the extent of many millions of dollars annually—250,000,000 in 1943, I am told—money which would go a long way in psychosomatic medicine. Apparently we must exhaust our credulity in regard to this cause of illness as we have with "focal infection" and "autointoxication."

#### THE PSYCHOSOMATIC APPROACH TO DIAGNOSIS AND TREATMENT

If we are to be successful in teaching physicians to deal effectively with emotional problems in illness and disease they must be given a basic training and experience in psychopathology running parallel with their training in tissue pathology.

Like a wise and experienced gross pathologist who makes shrewd guesses from the gross appearance of the organs so may the experienced clinician make shrewd guesses from gross distortions of the personality. But he is in a much happier position if he knows the underlying structure of the personality. Such knowledge is now available, and gradually our medical schools are teaching it. Moreover this knowledge must become an integral part of medical thinking and an automatic part of the management of patients. In other words, the practice of medicine must really become psychosomatic and then the term will no longer be necessary. So far as general medicine is concerned brief psychotherapy must complement psychosomatic diagnosis.

Therefore from the moment that the general physician meets his patient he must be trying to differentiate or evaluate somatic disease and distinguish the early or borderline psychoses. Then he must be able to establish positive data in regard to the personality structure of the patient—the relationship of symptoms to conflict, the discovery of the secondary gain, and an understanding, if possible, of the choice of symptom. Only in this way can he stand on safe ground in regard to diagnosis and treatment. He must be able to know, for example, that if he attempts minor psychotherapy in an adolescent or in a patient with a tic he is dealing with as dangerous a situation as though he attempted minor surgery on an infected upper lip. As Lindeman (4) expressed it "poor psychiatry is as dangerous to the social life as a poor surgeon is to the physical life."

As a basis for the present paper a study was made of 100 consecutive patients encountered in the practice of internal medicine who were considered to be psy-

chomatic gastro-intestinal problems. Forty-four were classified as neurosis with gastro-intestinal symptom formation; thirty as somatic disease plus symptoms in part of emotional origin; fourteen as vegetative neuroses.<sup>2</sup> Seven cases fell in the group of psychoses with gastro-intestinal symptoms and five were labeled as hypochondriasis.

Among the neurotic cases with gastro-intestinal symptoms twenty-one were listed as anxiety states, sixteen as conversion neuroses, five as compulsive neuroses and two phobias.

#### INCIDENCE OF "FUNCTIONAL" DISORDERS

Thus, as is well known, every variety of personality from the well adjusted to the psychotic may have psychosomatic disturbances of the gastro-intestinal tract. As in other surveys (5) the percentage of somatic disease represents about one third of all cases seen. This leaves, so far as the gastro-intestinal field is concerned, about two-thirds of the cases in which the gastro-intestinal symptoms appear to be chiefly of psychogenic origin. There are many variations in this regard depending upon the bias of the observer. For example in the purely organic approach of diagnosis by exclusion, a study of a consecutive series of 15,000 patients with chronic dyspepsia examined in the Mayo Clinic showed a total of 18 per cent to be the result of gross organic diseases of the stomach and duodenum. In commenting upon this material Eusterman (6) stated that these and a few other rare lesions, would account for about 21 per cent of the cases of chronic gastric disturbances. But he added that in private general practice the percentage might not exceed 10. He concluded that gastric disturbances arising reflexly from abdominal viscera other than the stomach are responsible for from 30 to 40 per cent of all cases and that in his opinion the neuroses constitute about 25 per cent of the total. Interesting also in this connection was an effort to test the accuracy of the diagnosis of nervous indigestion. Wilbur and Mills (7) studied the records of 354 patients who after examination at the Mayo Clinic received the diagnosis of functional or nervous indigestion or its equivalent and who were reexamined at the clinic more than seven years later. In 303 cases no evidence of organic disease was found in the follow-up examination. The results suggest a diagnostic accuracy of at least 85.6 per cent for functional dyspepsia in that series. There were thirty-nine cases in which organic disease of the gastro-intestinal tract was found at subsequent examination, but in nineteen of the thirty-nine a final diagnosis of duodenal ulcer was made and this represented the most common diagnostic error in the series. I need not comment on whether this represents a serious error in view of recent psychosomatic studies regarding the etiology of peptic ulcer.

Thus when chronic dyspepsia is approached even from a purely organic standpoint the incidence of functional disorders is at least 25 per cent. I have commented previously on the inadequacy of this type of investigation which

<sup>2</sup> A distinction is made between somatic disease with emotional factors, such as structural alterations of the gall tract with stone formation, and the vegetative neuroses. In the latter are included cardiospasm, peptic ulcer and ulcerative colitis.

represents diagnosis by exclusion. Diagnosis of "functional illness" must be established not simply by exclusion of organic disease but on its own characteristics as well. In other words, *neurosis has its own distinctive features to be discovered by personality study*. Only in this way can serious errors in diagnosis and treatment be avoided. If this is true then it must naturally follow that personality studies are just as important in the problems of chronic dyspepsia as laboratory investigations. This applies not only to problems in which evidence of structural disease has been excluded but also to patients who present evidence of physical disease and emotional factors. Just as we cannot limit ourselves simply to the exclusion of organic disease in the so-called purely functional group, so even more importantly is there the necessity for study of the emotional life in patients who present evidence of an organic lesion. The "either-or" concept in medicine must be displaced by the idea of how much of the problem is psychological and how much of it is physical and what is the relationship between the two.

#### PSYCHOSOMATIC DISTURBANCES

Of a great number of clinical syndromes among the psychosomatic disturbances of the gastro-intestinal tract I can select only a few for special comment. For the most part I will choose the commonest problems in order to develop my thesis that psychosomatic thinking must become an integral part of the practice of medicine.

*Constipation.* Constipation and headache are among the most frequent symptoms confronting physicians in their daily practice. Probably the most frequently assigned cause of headache is constipation and it is obvious why this should be so. On the assumption that "obstruction" or "accumulation" leads to absorption of toxins from the gastro-intestinal tract which may prove poisonous, and that a symptom of such poisoning is headache, a great many sufferers from headache are addicted to the laxative, enema, or colonic irrigation habit. We cannot say that there is no such cause of headache but certainly it is overemphasized both by the laity and the medical profession and also exploited by drug houses, from the standpoint of advertisements for laxative preparations, and by institutes for colonic irrigations. Every physician has had the experience of observing patients who are constipated for many days and do not have headaches. They are also familiar with the headache victim whose headache disappears magically just as soon as the bowels move—too soon for a physiological mechanism to be responsible.

*Illustrative Case.* M. F., a white girl, aged 19, was first seen in the spring of 1942. She complained of constipation of several years duration, headaches, ulcers in the mouth, and atigue. She had never been seriously ill and there were no other symptoms of importance except that she had had enuresis until she was 16. Her father and mother had never been compatible and the patient had always been aware of tension in the household. Finally the parents separated and the four children, of which our patient was the youngest, remained with the mother. At this time the enuresis ceased.

The general physical examination showed no evidence of disease and it quickly became apparent that more important than the symptoms complained of was a high degree of social

anxiety in a hysterical person which had interfered with her social development. From a genetic standpoint, insecurity in personal relationship was of course related to the insecurity of childhood and the constipation apparently was a reflection of the tension growing out of social situations. One such situation which seemed to cause the most trouble was an attempt to compete with a pretty cousin. Anticipation of such competition would bring about headache and constipation which were aggravated by erroneous ideas regarding bowel obstruction and toxic poisoning.

The origin of the symptoms was made clear and when she was reassured about the insignificance of the constipation and encouraged by the physician, who assumed the rôle of a friendly parent in trying to give her a little more self confidence and urging her to cultivate new interests and friends, she improved remarkably and blossomed out into a friendly creature who in turn "found everybody more friendly." Incidentally constipation no longer was a problem.

During a period of a year and a half her progress continued and then suddenly new symptoms appeared. She suffered from vertigo and had pain in the epigastrium. It was not difficult to ascertain that she was forced again to compete with a very attractive young woman in a new circle of boys and girls in which she felt insecure. Once more a single interview succeeded in pointing out the source of anxiety and permitted once again the opportunity for more reassurance and the acquisition of more self confidence.

Here, without mentioning psychotherapy, the physician assumed the parental rôle, taking the attention of the patient away from the symptom and attaching it to life circumstance. It would be fine for this young woman to have the advantages of psychoanalysis but since that is clearly out of the question we must get along with less. There is no question that transference played the important rôle and was deliberately utilized. Re-education regarding the workings of the body and some insight regarding the growing pains of delayed emotional development were the basis of the brief and in this case superficial psychotherapy although of course psychotherapy does not have to be superficial just because it is brief. There is no question either that the patient remains dependent on the physician and will have to return from time to time as she encounters new situations. Is it not better, however, to treat a patient with constipation in this manner rather than to make this young woman dependent upon laxatives or enemas and perhaps start her on a career of gastrointestinal invalidism. So often we find the criticism leveled at the psychotherapist that he does not cure people—they remain dependent upon him. No one expects the diabetic specialist to cure his patient—when he regulates the diet and adjusts a dosage of insulin and carries his patient along successfully everybody is satisfied. Why cannot the psychotherapist be permitted the same privilege of administering reassurance and enlightenment in regulated dosages knowing full well that in the greatest number of instances he cannot hope to achieve cure but instead strives to make the patient a healthier, happier and more efficient individual.

*The Male Climacteric.* Only a little less abused than vitamins are the endocrine products in the present day practice of medicine. With the increased interest of the medical profession in endocrinology and the exploitation of this interest by pharmaceutical houses in marketing endocrine products, a new flood of lurid literature has crossed the physician's desk on what is termed the male climacteric, or even less aptly the male menopause. Anything that hap-



pens to a man of 50 that cannot be accounted for on the basis of physical disease is now apt to be blamed on gonadal insufficiency and he then gets a series of expensive injections of testosterone. It is the exact counterpart of the problem in the female whose functional illness around the age of 45 is blamed on menopause and treated with estrogens. How to separate fact from fiction in these problems is indeed difficult but I submit that we have not yet reached the stage of an accurate manipulation of instinctual balance with endocrine products. Perhaps the time will come but it is not yet here. Meanwhile I recommend scientific psychotherapy in addition to or in place of endocrine therapy.

The male climacteric is said to be characterized by nocturnal urinary frequency, fatigue, indecision, hot flushes, and decreased libido. Other symptoms such as vertigo, mood changes, headaches, gastrointestinal symptoms, a feeling of inadequacy in undertaking new duties, and a tendency to seclusion are sometimes included as a part of the syndrome.

Most of these symptoms have been conspicuous in the psychoneuroses. Certainly they often arise from emotional conflict, and can be effectively treated by psychotherapy.

*Illustrative Case.* R. K., a white man of 53 was first seen in 1935. He had an acute respiratory illness from which he made a quick recovery. The illness afforded the opportunity of getting acquainted with the patient. He had always been a teacher in a small town and had one son, who had referred the patient to me.

I did not hear from him again until 1940, five years later, when he stated that he had been listless and tired for the past several months and had had some attacks attended by sweating and nausea but no vomiting. In addition there were some dizzy spells in the morning and one rather severe attack occurred in a physician's office two weeks before.

Reviewing his history he stated that he had been well for the past five years, had been working hard, smoking moderately, taking an occasional drink. For the last two or three years there had been a gradual diminution in his sex desires—"it had never meant much to him."

The physical examination was negative except for slight elevation of the blood pressure which had not been noted five years previously. There was slight tremor and on further questioning the patient stated that he had become a little more intolerant to heat and somewhat irritable.

In my note of that visit I observed the following familiar, differential diagnostic problem with which I was concerned at the time, namely—anxiety neurosis, so-called neurocirculatory asthenia, mild hyperthyroidism and, in relation to the whole problem, the question of the male climacteric.

Ordinary laboratory studies were negative and basal metabolism was within normal limits.

The son told me that his father had been getting more irritable during the past year and suggested that he was worried about the future. On that basis I began the discussion using the illustration of "body language"—that dizziness and vertigo may be the body's physical expression of insecurity. He said that since the new governor had come into office a bill had been passed forcing the retirement of teachers at the age of 62 and in his case this would provide only a small pension which would be insufficient for him and his wife to live on. He had invested all of his money in his son's education and wondered whether the son would be willing and able to take care of them. As he discussed this problem he became very emotional and it was obvious that this was the point that was disturbing him. I spoke about the son's future and the fact that he wouldn't let his father down and then reassured him as to the absence of organic disease.

He remained well for more than three years. Then he began to lose weight, and became worried and fretful. The physical examination showed frequent irregularity in the heart rate, and the electrocardiogram indicated early evidence of myocardial disease. Otherwise the examination was negative and basal metabolism was still within normal limits. The patient was smoking heavily. His wife's illness and the necessity for looking after her himself "had been too much for him." But his son had entered the service and this had reactivated his insecurity.

*Comment:* Here was an average man reacting to stress and strain by presenting some of the psychic, sexual and vasomotor disturbances that are sometimes associated at this period of life and are now often referred to as the male climacteric. Whether they should be is not so much the question except in so far as it bears upon treatment. In general it may be said that too much is apt to be blamed on the menopause, just as in the woman, and treatment is apt to be restricted to endocrine products. In this case very simple psychotherapy did a great deal. It was the kind of psychotherapy that any physician should administer and it doesn't have to be called psychotherapy. It is simply a normal part of the physician-patient relationship but it depends upon a knowledge of psychopathology. Here too we see the necessity for equal attention to tissue pathology as we watch this middle-aged man developing degenerative heart disease which of course will also enter into the question of his emotional problems to produce indissoluble psychosomatic relationships.

*Anxiety States.* Anxiety states with gastro-intestinal symptoms are the commonest of all psychosomatic problems. The most frequent rationalization of anxiety in gastro-intestinal problems is *cancerphobia* and in a way it represents a crude index to the severity of the neurosis. The intensity of the fear, the degree of reassurance necessary to abolish it, and hence the frequency with which it returns, and the capacity for enlightenment, serve as clues to the differential diagnosis so that usually it is not too difficult to tell whether one is dealing with a simple anxiety state or a border line psychosis. In the ordinary case the cancerphobia frequently makes its appearance at the end of a medical examination when the patient laughingly states after reassurance: "I am so relieved because I thought I might have a cancer." Brief psychotherapy finds its greatest usefulness in the milder anxiety states and where conversion mechanisms are concerned an approach based on "organ language" often permits a ready access to significant psychological material. One of the difficulties that I have experienced is that too much mental catharsis in severe anxiety states proves disturbing rather than helpful to the patient.

#### DEPRESSION AND "GASTRO-INTESTINAL MANIFESTATIONS"

Much has been written on this subject but the general physician cannot too often be reminded of the necessity for recognizing the mood disturbance underlying the gastro-intestinal symptoms. This is very often true in the so-called "colitis" cases. An irritable colon, dependent upon emotional factors, is the usual mechanism as it also often is in the so-called non-calculous gall bladder disease. Suicides, totally unlooked for by the general physician, are sometimes

the sorry aftermath of a long period of bowel treatment and gall bladder drainage.

*Hypochondriasis.* Five of my patients were classified under this heading and, as was to be expected, were the least amenable to brief psychotherapy. An interesting example, reported elsewhere, (8) illustrates an important aspect of this problem.

*Illustrative Case.* A very obese, hypochondriacal, middle-aged, white woman had been obsessed for several years with the idea that she had cancer of the throat and despite the reassurance of many physicians who had studied her carefully, she continued to believe "that there must be some physical basis for the pain and burning sensation in the back of the throat." She also had a great fear of infection, was meticulously clean about her home, and was forever washing her hands. She was very insistent about having something done for her throat and she herself would make topical applications of irritating solutions until, on many occasions, bleeding occurred. Even this did not satisfy her need for suffering so that she finally succeeded in persuading a dentist to remove her perfectly good teeth. She encountered less difficulty in sacrificing her tonsils. Both operations gave temporary relief but the symptoms returned worse than ever. She was so fixed upon her physical symptoms that it was impossible to accomplish more than the most superficial investigation of her life situation. The only digression she would make from a discussion of her physical symptoms was to upbraid her local physician for fancied mistreatment and insulting behavior. He had sent her to me for a general diagnostic survey but continued to supervise her care. She spent a great deal of time criticizing him for a lack of interest in her condition and for the "contemptuous way" in which he treated her. Nevertheless, it was obvious that underneath the surface hostility there was a very positive attachment to her physician which was indicated by her continuation under his care and by such statements as "she had great faith in his scientific ability; on occasions he had been very kind to her; and her children and her husband were devoted to him."

She was a very religious person and went to church every morning seeking help for her illness. On one occasion she went to seek help in making a decision on two related questions, first whether finally to quit her physician and seek another and secondly, whether for financial reasons it would be better to give up a health insurance policy which provided nursing service in case of a confining illness. She had carried this costly policy for a long time without realizing benefits and now her funds were low. On the particular morning in question she prayed for help in making these two decisions. As she left church she noted that it had been raining and while ordinarily, because of her overweight, she took special precautions in descending stairs, "she was not as careful as she should have been" and on reaching the third of three steps, slipped on a wet spot, fell and fractured her left ankle. As she explained to me on the telephone the next day, "she got her answer quicker than she thought." She seemed in a cheerful frame of mind as she told me, with evident satisfaction, that her physician had immediately responded to the call after this accident.

*Comment:* Aside from the purposefulness of the accident the marked ambivalence for her local physician was the striking feature of this case. Just as many neurotic people take up much time in criticism of some member of the family, just so did this woman express herself toward her physician. On the surface she was markedly hostile and yet she continued under his care and obviously held him in great respect and even with some evidence of underlying affection. He found the patient a very disturbing factor in his practice and confessed to me that when it was necessary to see her "it made a wreck out of him." When the psychological background of the relationship was explained to him, he found

matters a little easier, but needless to say, was pleased when the patient finally made up her mind to place herself under the care of an older physician who had "taken care of her in childhood." Because, to conclude the story related above, once the fracture had healed, she was back once more with her old throat complaint and criticism of her local physician.

The ambivalent relationship to her physician, so excessive in this particular instance, is a very important element in the doctor-patient relationship, as yet not understood in general medicine.

#### VEGETATIVE NEUROSES

*Cardiospasm.* Much has been written about the vegetative neuroses elsewhere (9) so that I will confine myself to a brief statement regarding cardiospasm which I have had a special opportunity to study through the kindness of the Chevalier Jackson clinic at the Temple University Hospital. Although a rare disorder it has many important relationships to other functional disturbances of swallowing and to the feeding process in general. Moreover, if evidence were forthcoming in favor of the psychogenic origin of even some cases of cardiospasm it would aid in establishing the important concept of the rôle of psychogenesis in the determination of physical disease. An article on the subject has been published in a recent issue of the journal, *Psychosomatic Medicine* (10), to which I will only add that these severe organs neuroses do not respond very satisfactorily to brief psychotherapy. Like *anorexia nervosa* they represent severe personality disorders and while I think it is highly desirable to study them psychologically we cannot hope to alter very much the profound psychological disorder which in turn is associated with a pronounced physical disorder. It is truly a condition in which psychosomatic diagnosis and treatment are essential. To treat such patients by psychological methods only is not enough nor is it enough to treat them only by means of dilatation of the lower end of the esophagus, which is the usual procedure. Both methods are necessary in the average case.

#### SOMATIC DISEASE PLUS EMOTIONAL FACTORS

The most complicated of all psychosomatic problems of the gastro-intestinal tract and the most important from the standpoint of the difficulties that one may get into are the physical disorders complicated by emotional problems. Peptic ulcer and its complications of perforation and hemorrhage, gall tract disease with calculous formation, ulcerative colitis and diverticulitis, not to forget cancer with its insidious development are some of the common problems. Even more complicated are the associations between the gastro-intestinal tract and the cardiovascular system. The following case will illustrate some of these problems.

*Illustrative Case.* H. G., a white man of 50, first consulted me in 1929. He complained of pain in the epigastrium. This had made its first appearance about three years before when he noticed a pressure-like sensation. No abnormality was detected in the physical examination except a few bad teeth. These were removed and the patient was advised to



stop smoking and his digestion improved. He was not heard from again until 1935 when he complained of fullness after meals. Again no abnormalities were detected except slight elevation of the systolic pressure. At the same time he spoke of being short of breath on exertion but only after breakfast. This again seemed to be a pressure-like sensation rather than dyspnea. However, because of this symptom, special attention was paid to the cardiovascular system but clinical, x-ray and electrocardiographic examination did not reveal any abnormality. When a short time later, x-ray of the gastro-intestinal tract showed a typical duodenal ulcer deformity and the possibility of additional esophagitis—on the basis of a rather spastic esophagus with evidence of hyperactive peristalsis—attention was directed away from the cardiovascular system.

The patient was a very reserved and passive individual with pronounced feelings of inferiority. He had a neurotic and nagging wife, and two daughters, one of whom was hysterical. In addition he had had financial difficulties and it was felt that all these factors entered into his digestive problem. A dream of being in a department store where he could not find his way and nobody could help him led to a discussion of his fear of losing his job and the fact that he was "up against it."

With superficial psychotherapy and certain general medical measures, such as diet and sedation, he improved somewhat but continued to have the pressure-like, choked-up feeling, especially in the mornings. Between 1938 and 1941 he was much improved although the symptoms never left completely. In 1941 he returned—the symptom was less pronounced but the blood pressure was elevated and the electrocardiogram showed changes. X-ray showed that the duodenal ulcer had completely healed and there was no further evidence to suggest esophagitis. Attention once more was focused on his cardiovascular system as well as upon his psychological problems.

His daughter's marriage had ended in divorce, his wife was becoming more and more difficult and for the first time he confessed that he had been "sexually frustrated" for years. In a resigned voice he said "what's the difference" but showed considerable hostility in his feelings.

In 1942 he had a slight attack of congestive heart failure and was sent to the hospital where he made a good recovery. After this he remained at home for several weeks but he was very depressed and complained of headache and nausea. His blood pressure had been steadily rising over the years and he now showed persistent hypertension. His daughter wrote to me that he was so disconsolate that they did not know what to do with him at home and urged me to give him a "pep talk." On his next visit to me I talked to him on the necessity for cultivating a fighting spirit. He walked out of the office apparently feeling better and when he got home his family remarked on his improved spirits. That night, after retiring to his room at the usual time, the family heard a thump on the floor and ran up to find that he had collapsed. Apparently he had died instantly. Fortunately for my peace of mind he had not exerted himself after his visit to me. The family assured me that he had done nothing unusual. If he had I would have felt that it was a very misguided "pep talk" indeed.

#### SUMMARY

A very passive, inhibited man with pronounced feelings of inferiority, complained of indigestion and pressure under the sternum. He was studied carefully to exclude heart disease. Duodenal ulcer and esophagitis were demonstrated. Emotional factors seemed important. The ulcer healed, but hypertension developed; progressive myocardial changes occurred, and sudden death happened to follow a "pep talk" for depression.

This case once more emphasizes the importance of angina pectoris as a cause of death and, also, the difficulties in diagnosis that are sometimes encountered. Because of the negative cardiovascular findings and the positive gastro-intes-



tinal findings it was decided in the early years of his illness that a digestive disturbance, in which emotional factors entered, was wholly responsible for his illness. Later, however, when there was evidence that the ulcer had healed and there was no longer any suspicion of esophagitis and, at the same time, positive evidence of cardiovascular disease appeared, the diagnosis was reversed although we could never be certain that some functional disturbance of the gastro-intestinal tract on an emotional basis was not also present. By chance an interview dealing with brief psychotherapy coincided with sudden death from heart disease.

I would have liked to deal with many other clinical syndromes but time permits only the briefest mention of a few.

*Hypoglycemia.* Hypoglycemia in relation to gastro-intestinal symptoms is a frequent diagnosis nowadays. I will only mention in passing that "low blood sugar" like "low blood pressure" is often held responsible for a state of fatigue when the hypoglycemic state is so often only a part of the mechanism of the psychosomatic reaction—the psychological response to emotional stress. Occasionally indeed it is a primary defect, as in island tumors of the pancreas, but usually it is only a secondary symptom.

Many patients with fatigue and gastro-intestinal symptoms have *low fever* of obscure origin and all of the attention is centered on finding the cause of the fever. Formerly such patients were often thought to have early tuberculosis and frequently spent long periods in sanatoria. Now chronic brucellosis is apt to be held responsible.

In dealing with patients of this kind we must map out a program of investigation, prosecute it actively and then within a certain limited time, having assured ourselves that there is no organic disease present, say to the patient, "you do not have organic disease, the slight fever is not important, throw your thermometer away and let us get after the cause of the fatigue because that is your important problem."

What is more important than whether we term the fever itself psychogenic is to realize that the fever is not the most important part of the problem but simply represents one phase of a disturbance in the constitutional make-up of the individual of which the disturbance in the emotional life represents another and more important phase. More important because the patient frequently derives great benefits from an improvement in the life situation brought about by brief psychotherapy.

*Polysurgical Addiction.* The chronic gastro-intestinal invalid with a battle-scarred abdomen of *polysurgical addiction* (11) is fortunately not quite so common now because surgeons are becoming a little more wary of operating for exploratory reasons. "The unconscious will to remain sick" is a very important consideration in medicine and in this kind of patient is of paramount importance. Such patients are eager to be operated upon and in their insistence upon the continuous and excruciating nature of the pain from which they suffer one can easily understand how a very sympathetic surgeon may be prevailed upon to operate. This is particularly true when such patients meet

surgeons who are not loath to operate. Thus, we can say that a willing and even eager patient, who derives a certain satisfaction from being hospitalized and and operated upon, and a surgeon who is ever ready to wield a knife is a very unfortunate combination. A great many patients with numerous scars on the abdomen serve as testimony to this combination.

The question of *psychological preparation for surgery* is one of the major problems in medicine. Surgeons are always so careful to prepare their patients physically for surgery; they would never think of performing a major operation without knowing that the cardiovascular-renal system has been surveyed but they almost never give any consideration to the kind of personality that exists in the individual who is about to be operated upon; how much anxiety is there, and what the effects of a surgical traumatic experience may be as far as the personality structure is concerned. We recently had in the hospital ward a woman with an enlarged thyroid gland which was removed because of "smothering" sensations. No effort was made to study her psychologically. The anatomical problem loomed large in the clinical picture but the patient was very apprehensive prior to operation and after operation became completely psychotic. I wonder whether perhaps she was not better off with the lump in her neck. Similar instances in abdominal surgery are all too common.

#### CONCLUSION

Psychosomatic diagnosis complemented by brief psychotherapy must become an integral part of the practice of medicine. This does not mean to study the soma less; it only means to study the psyche more. Gastro-enterology especially must incorporate this approach. Recent experiences in military medicine emphasize these points.

So far as gastro-intestinal problems are concerned this kind of an approach will permit the physician to realize that the abdomen is the sounding board of the emotions; from a dynamic standpoint he will learn that bed and board are as indissolubly linked in the emotional life of the adult as are sustenance and sensuality in the life of the infant; and from a genetic standpoint he will discover that the real social disease is in the atmosphere of the home where the foundation is laid for many of the gastro-intestinal ills of mankind

#### REFERENCES

- (1) FRIESS, E. C., AND NELSON, M. J.: Psychoneurotics Five Years Later, *Am. J. M. Sc.*, 203: 539, April, 1942.
- (2) LEVINE, M.: Discussion of Techniques, First Brief Psychotherapy Council, Inst. Psychoanalysis, Chicago, p. 37, 1942.
- (3) ALVAREZ, W. C.: Nervousness, Indigestion and Pain, New York, Paul B. Hoeber, Inc., 1943.
- (4) LINDEMANN, E.: Therapeutic Procedures in Psychoneurosis, *New England J. Med.*, 227: 584, 1942.
- (5) WEISS, E.: Personality Study in the Practice of Internal Medicine, *Ann. Int. Med.*, 8: 701, 1934.
- (6) EUSTERMAN, G. B.: Diagnostic Aspects of Roentgenologically Negative Gastric Disorders, *J. A. M. A.*, 107: 1232, 1936.

- (7) WILBUR, D. L., AND MILLS, J. H.: How Accurate Is The Diagnosis of Functional Indigestion?, *Ann. Int. Med.*, 12: 831, 1938.
- (8) WEISS, E.: A Brief Note Regarding A Purposeful Accident, *Psychosomatic Medicine*, 2: 4, 1940.
- (9) ALEXANDER, F.: (a) Fundamental concepts of Psychosomatic Research: Psychogenesis, Conversion, Specificity, *Psychosom. Med.*, 5: 205, July, 1943.  
(b) Gastrointestinal Neuroses. In PORTIS, S. A.: *Diseases of the Digestive System*, Philadelphia, Lea and Febiger, 1941.
- (10) WEISS, E.: Cardiospasm: A Psychosomatic Disorder, *Psychosom. Med.*, 6: 58, 1944.
- (11) MENNINGER, K.: Polysurgery and Polysurgical Addiction, *Psychoanalyt. Quart.*, 3: 173, 1934.

## MAN HIMSELF THE CHIEF PROBLEM IN CARDIOLOGY<sup>1</sup>

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Man enters into cardiology in three ways. In the first place, the patient himself is an individual who is born with or later acquires individual characteristics of cardiac and vascular tissues, not only in structure and function but also in their reactions to environmental conditions and strains. It is of this that I shall speak chiefly. Secondly, the patient is a human being of a certain variable amount of nervous sensibility and intelligence who may or may not feel or be able to relate what is wrong with him. And thirdly, last but not least, the doctor is likewise a human being of variable innate ability and energy and acquired training, who may or may not possess the art of obtaining from the patient all the information by word of mouth, by physical examination, and by laboratory tests that may be needed to complete the picture, to solve the problem, and to institute proper treatment. All the book knowledge in the world, all the most elaborate equipment, and all the skill in the use of that equipment may fail in securing answers to many of our most interesting and important questions in cardiology, both in the individual patient and in the science at large.

And so at the threshold of your new institute I would like to see you utilize and emphasize in fullest degree not only the beautiful physical arrangements that you have prepared but the even more important, though sometimes seemingly intangible, technics of dealings of doctors with patients and of study of symptoms and mental reactions that have been even at the present day but partly explored. Patient training, experience, and by direct apprenticeship the passing on of the so-called art of medicine will continue to bear the richest fruit. Actually such is not art but science in the truest sense of the word, that is, the knowing how to get information by word and thought, to secure the cooperation of the individual, and to have him accept and persist in the proper treatment. Such cooperation secured is of inestimable value in the follow-up of patients, including examination post mortem, which in the rush and hurry of today is so often neglected and replaced by quick, poorly controlled studies that flash into our vision for a moment and disappear as quickly. After thirty years of experience in this field, I have become convinced of the importance of the special technics of the dealings of doctors with their patients which can be better taught than is as yet the custom.

Now let me turn again to the patient himself as an individual human being who is endowed with heart and blood vessels that may be normal or diseased. The first of several points, and I believe the most important, that I would stress is the *range of the normal*. By all odds, this fundamental knowledge which should be our richest inheritance in cardiology is our Achilles heel. We remain woefully ignorant about the normal in structure and function, not in some specific instance perhaps, but in the limits of normality. Herein two factors

<sup>1</sup> Presented at the inauguration of the Instituto Nacional de Cardiología, Mexico City, April 19, 1944.

play the major role: 1) *inheritance* which predetermines to a large extent size and shape of heart, its electrocardiographic pattern, its autonomic nerve control, blood pressure level and reaction, and the degree of myocardial and coronary reserve; and 2) *environment* which can alter appreciably by the interaction of various factors of strain or their absence the inborn characteristics just mentioned. Let me give you some examples. Identical twins have almost exactly the same size and shape of roentgen heart shadows and heart weights as they have the same size and shape of nose, and their electrocardiograms are closely similar. It is probable that there is more or less of a characteristic family coronary tree, which may be in part responsible for the common affliction or even commoner escape of many families from angina pectoris and myocardial infarction—here alone is a fascinating field for study. There is even a family pulse rate.

Just as families tend to show similarities of structure and function so strangers of the *same body build* resemble each other in a cardiovascular way, though not so closely as do identical twins. It is not a matter solely of height and weight or body surface; there are other measurements, for example, length and width and depth of thorax and of abdomen, girth, and length and size of arms and legs, size of bones, and other physical characteristics that need appraisal in our search for adequate correlations, which we still lack, of heart size and function with the individual man himself. Here indeed is rich soil for anatomical and physiological research on which much of our superstructure of medical knowledge and practice must rest.

Moreover just as there are family and body type similarities as applied to the heart and circulation so there are certain *resemblances acquired* as the result of certain extrinsic factors. Let me cite a few. The trained athlete in training tends to have a slow heart rate at rest, often in the 50's and the 40's, and even in the 30's in the case of a few long distance runners. The resident of very high altitudes develops certain physiologic and even anatomic characteristics as the result of the low oxygen pressure: a compensatory polycythemia, cyanosis, clubbing of the fingers, a barrel chest, and pulmonary emphysema. I have found in a few men who have swum under water vigorously for years a physiologic fullness of heart size with prominence of right ventricle akin to the porpoise heart by which term I have designated this condition in man. Residence in the tropics is said to lower the blood pressure, perhaps because of the inertia inherent in such life. Thus the physiologic acquisition of certain modifications of cardiovascular structure and function is also a field of study that promises well. In such a study climate and altitude, work and sport, food and habits all may need scrutiny. The whole world is full of nature-made experiments which can be studied as they are or modified by man for further analysis.

Now let us turn to heart disease and pathologic states of the circulation to see how these same principles may apply thereto. At the beginning of life are the various *congenital defects*. There is not as a rule, so far as I know, a particular body build that carries with it congenital heart disease except for the rare arachnoidactyly which is attended most often by an auricular septal



defect. It is true, of course, that certain anomalies such as the tetralogy of Fallot and high degrees of patency of the ductus arteriosus may retard growth and normal development, and that there is something of a family tendency to congenital defects.

On the other hand, *rheumatic fever* and *rheumatic heart disease* have a very clear limitation to certain individuals; they do not occur in all persons exposed to or made sick by the hemolytic streptococcus. There seems always to be a relatively small group of persons who react, as if in an allergic way, to the streptococcus by developing rheumatic fever. It is an inherited predisposition, not active during the first few years of life but at its peak from 5 to 12. Unfavorable environment and climate act in a less important way by effecting the exposure of the susceptible person to a greater number of virulent bacteria under conditions of poorer general health. Although the obvious point of first attack in the ultimate control of rheumatic heart disease is that of excluding so far as possible contact of susceptible persons with the hemolytic streptococcus, the individual himself should not be forgotten. It is even possible that in the long run some method may be found to desensitize him so that he may encounter his hereditary enemy with safety.

*Subacute bacterial (infective) endocarditis* likewise does not attack everyone with congenital cardiovascular defects or the lesser rheumatic valve lesions. Here again there may be some individual difference either in lack of resistance to the *Streptococcus viridans* or in a tendency to thrombus formation on scarred valves or congenital defects. It hardly seems as if bad luck alone would be responsible. More study of the host as well as of the invading organism and its ravages is certainly in order in this dread disease.

*Cardiovascular*, that is, primarily *aortic*, *syphilis* is another type of circulatory disease that needs a word about the individual's so-called susceptibility. Many persons with syphilis never have any involvement of the aorta; others though but lightly infected have very vulnerable aortic walls; it is true that in such cases strenuous effort favors the development of dilatation, aneurysms, and eventual rupture, while antisyphilitic treatment and avoidance of strain favor longevity. It has also been noted that in some regions, Arabia for example, syphilis, though almost universal, seems to be so attenuated that there occurs little serious involvement of the aorta.

The *cor pulmonale* of high degree in *chronic* form is most common among stone cutters; there it would seem that the environment, that is, the job, is inherited rather than the susceptibility, although even here fellow workers vary considerably in their lung involvement. In lesser degree chronic pulmonary fibrosis is a cause and that may be in part at least attributed to an individual or family tendency to acquire chronic or recurrent lung infections. The *acute cor pulmonale* dependent on massive pulmonary embolism occurs more frequently in patients who have defective local circulations in their legs with a tendency to easy thrombosis in the veins.

One of the most striking instances of all of individual, in reality familial, tendency to heart disease deserves especial emphasis, namely the *essentia*.

*hypertensive* state. Precisely the same living conditions will, in one man or woman be endured with equanimity and normal blood pressure, while another will become hypertensive. Overweight, nervous strain, and excessive tobacco will aggravate existing hypertension or the tendency thereto, but they are not the fundamental causes. An inherited tendency to arteriolar spasm from causes not yet clear seems to be the answer. Heavy sedation if given before the establishment of extensive arteriolar sclerosis will reduce the pressure as a rule to normal or almost normal levels, but since living in a state of deep sleep is impracticable, an extensive lumbodorsal splanchnic sympathectomy has been developed by Smithwick successfully to control the pressure in the majority of the young hypertensives. But just what is this inherited fault in man and can it be bred out of the human race or in some other way prevented? This is a matter of major importance in all countries and demands your attention.

Finally, we come to another of the great cardiovascular hazards of our day and doubtless in unrecognized form of past history too, namely *coronary heart disease*. Here again two men living exactly the same life will differ widely. One will develop angina pectoris, myocardial infarction or electrocardiographic changes in middle age; the other will live to be very old without any of this. Why? There are a few clues but we haven't got very far along the trail. In the first place and most importantly the male rather than the female is an early victim; of 100 cases under the age of 40 years analyzed a few years ago by Dr. Glendy, Dr. Levine, and myself, 96 were men and only 4 were women. What is there in the masculine constitution or active principle that is responsible? Incidentally, in further corroboration of this fact it is common but neglected knowledge that the more robust (not necessarily fat) and masculine men, often outstanding athletes, are the more prone to develop coronary heart disease at an earlier age. There are very likely two other important factors that play a role in individuals or families: 1) the fullness of the coronary arterial tree with respect to richness of branches and anastomotic or potential collateral circulation, and 2) the metabolism and deposition of the cholesterol fats which at least in many cases appear to be the basic material behind the development of a crippling degree of coronary atherosclerosis.

Before concluding, there are two other conditions, not heart disease themselves but frequently confused therewith or functionally involving the circulation, that should be mentioned. The *arrhythmias*, in particular extrasystoles and the paroxysmal tachycardias, appear to show either a familial predisposition or at least a familial consciousness thereof due to a high degree of sensibility, or perhaps both. Even auricular fibrillation has been noted in several members of the same family, with or without heart disease.

The other condition is *neurocirculatory asthenia*, also called effort syndrome or DaCosta's syndrome, which more than any of the various ills already mentioned is dependent on the inborn or inherited constitution of the individual who presents characteristic symptoms of disorder of the autonomic nervous system under relatively little strain. I am not speaking of the acute temporary state due to excessive strain in the relatively normal stable person. A common

finding in neurocirculatory asthenia is the associated anxiety psychoneurosis and the family history of functional nervous disorders. It is this same type of person who shows an exaggerated reaction to real heart disease, for example, a sense of impending death in coronary insufficiency in addition to angina pectoris which is the real symptom of that condition, or even faintness or syncope therewith, a reaction which once induced Parry actually to write a book on the subject which he called misleadingly the "syncope anginosa". Good judgment and long experience permit an adequate appraisal of the relative responsibilities of the disease processes themselves and of the sensitiveness of the individual in the production of symptoms, but better instruction of the medical student and young physician than now exists should be instituted in this very important subject.

And so, in conclusion, let me plead for close attention to the factor of man himself in your study of the cardiovascular system and its diseases, man himself as a narrator of his own story, as an organism with symptoms that are sometimes more delicate evidence of disease than any produced by the most sensitive apparatus as yet invented, as an intelligent being who can cooperate with us, not only in his own treatment but also in our clinical researches and a long follow-up, and as a vital factor through inherited and acquired characteristics in the development of the various kinds of heart disease themselves. The study of heredity alone promises much yield and this is but one of many opportunities in the analysis of man himself.

## THECA CELL TUMOR OF THE OVARY IN A 72 YEAR OLD WOMAN

SEYMOUR WIMPFHEIMER, M.D., F.A.C.S.

Ovarian tumors which exert a hormonal influence have recently received considerable attention in the literature. Theca cell tumors of the ovary belong to this group. A feminizing effect such as atypical uterine bleeding and breast enlargement is produced by this tumor.

Since Loeffler and Priesel (1, 2) originally described six cases in 1932, and classified them as "Fibroma theca cellulare Xanthomatodes ovarii," many additional cases have been noted. Previously, some of these tumors were reported as fibromas or fibrosarcomas. In a review of ovarian fibromas, Geist and Gaines (3) found three belonging to the theca cell group.

The histogenesis of this tumor has been stressed by Geist (4, 5). He maintained that the theca cell tumors arose from the unused theca cells of the ovarian parenchyma. Another tumor belonging to this group of feminizing tumors is the granulosa cell tumor which Geist claimed was a distinct entity similarly originating from unused granulosa cells of the ovarian parenchyma. Novak (6) maintains a common origin for both tumors in the embryonic ovarian mesenchyme. He includes both under the designation of "feminizing mesenchymoma of the ovary."

Clinically it has been noted that theca cell tumors usually occur after the menopause. A case has been reported in a 92 year old woman by Patterson and McCullagh (7). They are always unilateral, not very large, not associated with ascites and usually benign. However, three cases of malignant theca cell tumors have been reported by Loeffler and Priesel (1, 2), Huber (8), Geist and Gaines (3). The coincidental occurrence of uterine fibromyomata, dermoid cysts and serous cyst has been noted. The symptoms produced are those of hyperestrinism, such as uterine bleeding and enlargement of the breasts. The uterus becomes enlarged and soft and the endometrium becomes hyperplastic. The symptoms all regress after removal of the tumor.

To explain this symptom complex, Melnick and Kantor (9) suggested that these theca cell tumors were able to produce estrogen. Geist and Spielman (10) did assay one such tumor and were able to demonstrate one mouse unit of estrogen in each 0.75 gm. of tissue extracted, an abnormally high estrogen content.

Pathologically on gross appearance these tumors have a glistening thin capsule and are firm and fibrous, though some show a tendency to cystic degeneration. They vary in size from a peach to a grapefruit, the surface having a yellow tint. These tumors cut with considerable resistance resembling a fibroma. The cut surface is noted to be composed of varying sized islands having a diagnostic yellow hue and separated by dense white hyaline connective tissue. Small or larger cystic areas are occasionally noted resulting from liquefaction necrosis.

Microscopically two features are characteristic, first a large amount of con-

nective tissue showing a tendency toward hyaline degeneration and secondly a large number of fat containing epithelioid cells arranged in islands or strands surrounded and invaded by the connective tissue (4). The intracellular or extracellular lipid is double refractile in polarized light, consisting of cholesterol ester. It is probable that this lipid is the estrogen which in excess causes the feminizing syndrome. Since these tumors vary in their lipid content, the symptoms vary accordingly.

The following case demonstrates that even 21 years after the menopause, a feminizing tumor may activate an organ that has been dormant and clinically atrophic for many years.

*History:* L. M., (Adm. #516884), aged 72 years, widowed 11 years, was admitted to The Mount Sinai Hospital on February 20, 1944, with the chief complaint of vaginal bleeding, occurring 21 years after the menopause. The patient had 4 children, the youngest 30 years of age, and one spontaneous miscarriage at 4½ months, about 35 years ago. Until her menopause, the menstrual history was normal. A diagnostic curettage was performed 17 years ago, because of vaginal bleeding. No pathological report was available, and patient was told no further therapy was indicated. There was a recurrence of this bleeding four years ago, when the patient bled for 1 week and again 6 weeks ago, when bleeding lasted for one day and was followed by staining for 5 days duration. The present episode of vaginal bleeding began 5 days ago, and had become rather profuse. The remaining history reveals that the patient had a cholecystectomy 25 years ago, and also has been known to be a mild diabetic for several years. The diabetes has been controlled by diet without being supplemented by insulin.

*Examination:* The general physical examination revealed an elderly, well developed but thin woman, weighing 105 lbs., not acutely ill and showing no evidence of excessive blood loss. The blood pressure was 130 systolic and 80 diastolic. The heart and lungs were normal. The breasts were somewhat heavier than normal. On abdominal palpation, no abdominal masses were felt. The extremities were normal.

The gynecological examination revealed the following: A normal parous introitus. The cervix appeared normal, but blood was seen coming from the cervical canal. The uterus was retroposed, slightly enlarged and irregular. To the right and behind the uterus was a firm round mass about 8 cm. in diameter.

*Course:* The provisional diagnosis of Theca cell tumor or granulosa cell tumor was made. Carcinoma of the fundus of the uterus was also a possible diagnosis. However, because of the very prolonged history of intermittent vaginal bleeding with comparative good health of patient, an ovarian tumor, exerting hormonal influence was considered the more likely diagnosis.

A laparotomy was performed on February 21, 1944. The findings were as follows: The uterus was somewhat enlarged and contained a few small fibromyomata. The right ovary was enlarged four times its normal size, and containing a cystic portion at one pole and a solid portion at the other pole. The left ovary was atrophic.

In view of the findings a supra-cervical hysterectomy and bilateral salpingo-oophorectomy was performed. The cervix was left *in situ*, because inspection of the endometrial cavity revealed no carcinoma.

The post-operative course was uneventful. The diabetes was controlled by protamine insulin and regular insulin in decreasing doses, so that when patient was discharged from the hospital on the 13th post-operative day, insulin therapy had been discontinued.

The abdominal wound healed by primary union and pelvic examination on discharge showed a freely movable cervical stump and normal parametria.

The patient was seen six months after operation feeling well. There was no recurrence of the vaginal bleeding, and the breasts resumed their normal size.





FIG. 1. Microscopic section ( $\times 175$ ) of ovary showing epithelioid cells and plaques of hyaline connective tissue.

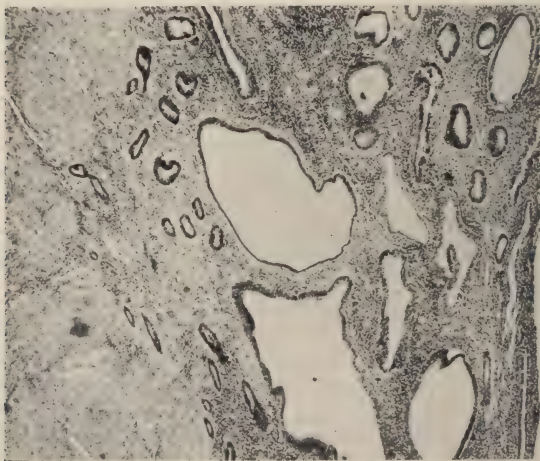


FIG. 2. Microscopic section ( $\times 52$ ) showing hyperplastic endometrium.

The Pathological Report (#P-27633), by Dr. Otani was as follows: "Adenomyosis and small fibromyomata of the uterus with hyperplastic endometrium. Theca cell tumor with cystic degeneration of right ovary. Atrophic left ovary.

"The gross specimen consists of a supracervically amputated uterus with left adnexa attached. The right tube and ovary are separately received. Uterus has previously been opened. The external surface is smooth and shiny. The endometrial surface is somewhat granular. The cavity measures 4.5 cm. in length and 4 cm. across at the height of the fundus. The endometrium measures up to 2-3 mm. in thickness and appears to have minute cysts within it. The wall is somewhat bulky, of even calibre and on section shows definite cystic structures within the wall predominantly close to the endometrial surface. There are in addition seedling intramural fibroids. The left tube measures about 12 cm. in length, the fimbriated end is freely patent. The left ovary is small, firm, gyrated, some-



FIG. 3. Microscopic section ( $\times 20$ ) showing adenomyosis of uterine muscle.

what yellowish in color. It measures 2.3 x 1.5 x 1 cm. and has previously been incised. On section it has a very definite yellowish overcast to the major portion which is not distinctly demarcated from the surrounding purplish stroma which contains a few corpora albicans. Separately received is the right tube and ovary. The fimbriated end is freely patent. The tube segment measures about 8 cm. The tube-ovarian ligament is smooth, thin. The ovary has previously been opened and incised. It is enlarged to about 8 cm. in diameter, in its present collapsed state. The external surface is everywhere smooth and shiny and there are areas of bright orange tissue shining through the surface. The opened ovary shows a cystic portion completely smooth walled with yellow orange tissue shining through the cyst wall. There is a solid portion to the tumor mass measuring roughly 4.5 x 2.5 cm. This area is moderately soft and composed of grayish white and yellow tissue."

The microscopic structure of the ovary (fig. 1) is typical of a theca cell tumor showing the fat containing epithelioid cells distributed in an irregular interlacing manner and separated by bands of connective tissue and hyaline plaques. The endometrium of the uterus (fig. 2) shows the effect of estrin stimulation. The glands are numerous, some cystic and lined by columnar epithelium.

The uterine muscle showed small bluish cystic areas which on microscopic examination proved to be adenomyosis (fig. 3).

#### SUMMARY

A case of theca cell tumor of the ovary is reported in a 72 year old woman, 21 years after the menopause. The feminizing effect produced uterine bleeding and enlargement of the breasts. The hormone effect was strong enough to stimulate the endometrium and adenomyotic areas which had been dormant for many years.

#### REFERENCES

1. LOEFFLER, E., AND PRIESEL, A.: Beitr. z. path. Anat. u.z. allg. Path. 90: 199, 1932.
2. LOEFFLER, E., AND PRIESEL, A.: Wien. med. Wchnschr. 84: 400, 1934.
3. GEIST, S. H., AND GAINES, J. A.: Am. J. Obst. & Gynec. 35: 39, 1938.
4. GEIST, S. H.: J. Mt. Sinai Hosp. 4: 821, 1938.
5. GEIST, S. H.: Ovarian Tumors. New York, Paul B. Hoeber, Inc., 1942, pp. 268-277.
6. NOVAK, E.: Gynecological and Obstetrical Pathology. Philadelphia, W. B. Saunders Co., 1941, pp. 344-356.
7. PATTERSON, J. H., AND McCULLOGH, W. McK.: J. Obst & Gynec. Brit. Emp. 43: 1186, 1936.
8. HUBER, HERBERT: Zentralbl. f. Gynäk. 61: 14, 1937.
9. MELNICK, P. J., AND KANTOR, A. D.: Am. J. Obst. & Gynec. 27: 41, 1934.
10. GEIST, S. H., AND SPIELMAN, F., J. A. M. A. 104: 2173, 1935.

## PEPTIC ULCER IN ADOLESCENCE: ITS RELATION TO PITUITARY DYSFUNCTION

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A great deal has been written about the incidence of peptic ulcer. Its actual frequency, as well as the distribution between the sexes and among the several age groups, has attracted much attention and aroused considerable dispute. A study of the data on this phase of the ulcer problem suggests the following conclusions: 1) Peptic ulcer occurs in 5 to 10 per cent of the adult male population; 2) duodenal ulcer is several times more frequent in the male sex; 3) peptic ulcer is not only less frequent, but a milder disease in females; 4) it is chiefly a disease of the third and fourth decades of life; 5) there are separate groups occurring, (a) in infancy, (b) in the puberty-adolescent period, (c) at the menopause, and (d) in old age.

Elsewhere we have discussed the relation of the ductless glands (particularly those secreting the sex hormones) to peptic ulcer (1). Herein we wish to present some specific observations, hitherto not noted, on the puberty-adolescent group of peptic ulcers. During the past few years we have collected a group of 24 of these cases (Table 1). They presented some unusual and striking features. All had duodenal ulcers. Gastric ulcer was not encountered in a single instance. This agrees with the general impression that gastric ulcer is found in older patients. Most of the cases fell between 12 and 15 years of age. Three were 17 and one was 11 years old. The symptoms were quite severe in most of the group. Five experienced massive hemorrhages. There were three perforations. Eleven with severe symptoms were subjected to partial gastrectomy.

The infrequency of the disease at this age, the severity of the symptoms, and a familial tendency to ulcer in this group has been pointed out by other observers (2). In our group, four had a familial incidence.

The most striking feature, however, remains to be brought out. This is the fact that simultaneously with the onset and early course of the symptoms, these boys grew rapidly, in most cases to an abnormal height. Ten of them grew to six feet; nine to five feet eleven inches, and five to five feet nine inches. All of them were not only the tall, but the thin type.

The significance of this association of rapid growth with peptic ulcer in this group of adolescent boys is at present conjectural. It may just be a coincidence. It will be necessary to collect a large series of peptic ulcer cases in the puberty-adolescent period in order to establish the statistical validity of this special group of cases.

There is also the possibility of a ductless gland relationship. At the adolescent period the sex hormones come into play, and the growth hormone is elaborated by the anterior pituitary gland. In the course of previous experience

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with this ductless glandular phase of the subject, we had noted the following (3): 1) In certain experiments in dogs, ulcerations about abdominal wall gastric pouch orifices increased (as well as the acid secretion in the pouches) during lactation. During oestrus, acid secretion lessened and the ulcerations healed. These observations indicated a possible relation of the anterior pituitary gland (involved in lactation) to the increased acidity and ulceration. 2)

TABLE 1  
*Record of some clinical features in 25 young males with duodenal ulcer*

| NAME          | AGE AT ONSET | PRESENT AGE | HEIGHT | RELEVANT FINDINGS   |
|---------------|--------------|-------------|--------|---|
| B. G. . . . . | 14           | 19          | 6'0"   | Moderate symptoms   |
| G. K. . . . . | 15           | 19          | 5'9"   | Perforation at 18   |
| N. K. . . . . | 15           | 25          | 5'11"  | Moderately severe symptoms  |
| B. L. . . . . | 15           | 29          | 5'9"   | Pyloric obstruction. Partial gastrectomy                              |
| W. B. . . . . | 12           | 17          | 5'11"  | Perforation at 17   |
| F. S. . . . . | 12           | 17          | 5'9"   | Moderate symptoms   |
| L. A. . . . . | 15           | 23          | 5'9"   | Eunuchoid features. Moderate symptoms                                 |
| R. F. . . . . | 14           | 19          | 5'11"  | Repeated hemorrhage. Partial gastrectomy. Father has ulcer            |
| O. V. . . . . | 17           | 23          | 5'9"   | Moderate symptoms. One brother with ulcer                             |
| P. M. . . . . | 13           | 30          | 6'0"   | Moderate symptoms   |
| J. R. . . . . | 14           | 18          | 6'1"   | One brother, 1 sister, 1 uncle with duodenal ulcer. Moderate symptoms |
| O. G. . . . . | 14           | 16          | 6'0"   | Both father and patient had partial gastrectomy                       |
| G. U. . . . . | 14           | 30          | 5'11"  | Partial gastrectomy for perforating ulcer                             |
| G. G. H. . .  | 13           | 22          | 5'11"  | Hemorrhage. 70 Free HCL. Partial gastrectomy. "Ulcer facies"          |
| M. V. . . . . | 12           | 52          | 6'2"   | Repeated hemorrhages. Partial gastrectomy                             |
| H. B. . . . . | 11           | 21          | 5'11"  | Obese. Polycythemia. Symptoms moderate                                |
| J. S. . . . . | 12           | 16          | 5'11"  | Symptoms rather severe. Marked hyperchlorhydria                       |
| F. N. . . . . | 13           | 25          | 6'2"   | Severe ulcer symptoms. Perforation and hemorrhage                     |
| J. K. . . . . | 17           | 33          | 6'1"   | Perforation. Later partial gastrectomy                                |
| S. A. . . . . | 15           | 36          | 5'11"  | Severe symptoms. Partial gastrectomy                                  |
| S. S. . . . . | 17           | 30          | 5'11"  | Moderate symptoms   |
| O. S. . . . . | 12           | 40          | 6'0"   | Gastro-enterostomy at 12. Two partial gastrectomies. Exodux           |
| D. K. . . . . | 12           | 44          | 6'0"   | Severe symptoms. Hemorrhages. Two partial gastrectomies               |
| A. K. . . . . | 13           | 24          | 6'0"   | Gastro-enterostomy, then partial gastrectomy                          |

The fact that peptic ulcer is predominantly a male disease; 3) that it is mild in the female; 4) that in the female it often commences at the natural or artificial menopause (anterior pituitary predominance?); 5) that ulcer in the female has its severest manifestations at or after the menopause, and 6) that estrogens may relieve menopause ulcer symptoms.

The bearing of these observations on the adolescent ulcer group herein described is patent. Both the rapid growth (modified gigantism) and the peptic ulcer may be associated with some abnormality in the functions of the anterior



pituitary gland. It would be of interest to study the androgens and anterior pituitary secretions quantitatively in these patients. Possible lines of therapy also suggest themselves. For example, estrogen (or androgen) administration to inhibit the anterior pituitary activity seems indicated.

With the exception of the height and thinness, we have noted no particular stigmas, such as acromegaly. Careful anthropometric observations, photographs and sella turcica radiographs could be collected.

Of course the possibility of the psychologic factor as an etiologic agent enters into the problem. During adolescence, emotional disturbances are common. We have not been impressed with this feature in our group, with the exception of one boy who harbored a terrific resentment against his parents.

We are not implying in this communication that peptic ulcer in general may be a pituitary disease. It is our opinion that, as emphasized chiefly by Eli Moscheowitz (4), in most of the adult group it is probably a psychosomatic disease. However, peptic ulcer may not be a unitary disease. For example, in the adolescent group a pituitary factor does indeed suggest itself. However, our chief purpose in presenting this interesting association of rapid, excessive growth with peptic ulcer in a group of adolescent boys is to stimulate further investigation.

#### SUMMARY AND CONCLUSIONS

Peptic ulcer is predominantly a disease of young adult males.

A group of adolescent boys with duodenal ulcer has been encountered.

The disease is quite severe in this group.

Rapid growth to abnormal height at the onset of the disease was noted.

This suggests a possible association between the anterior pituitary gland and peptic ulcer in adolescent boys.

#### REFERENCES

1. WINKELSTEIN, A.: A possible relationship between the ductless glands secreting the sex hormones and peptic ulcer. *J. Mt. Sinai Hosp.*, 7:1, 1940.
2. KALK, H.: *Das Geschwür des Magens und Zwölffingerdarmes*. Urban and Schwarzenburg, 1931.
3. WINKELSTEIN, ASHER: Observations on ulcerations adjacent to experimental gastric pouches in dogs. *Am. J. Digest. Dis. & Nutrition*, 3:4, 229, 1935.
4. MOSCHOWITZ, ELI: The psychogenic origin of organic disease. *New England J. Med.*, 212:603, 1935.

# THROMBO-ANGIITIS OBLITERANS AND DIABETES MELLITUS IN THE SAME PATIENT

## TWO CASES

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Thrombo-angiitis obliterans and diabetes mellitus are rarely seen together in the same individual. In the text books on peripheral vascular disease written by Buerger (1) and by Homans (2), the association of the two diseases is not mentioned. In contrast, considerable sections of both books are devoted to the discussion of the frequent association of arteriosclerotic peripheral vascular disease and diabetes. L. S. McKittrick, who has had considerable experience with diabetes and its complications states, "We have never seen the combination of diabetes and thrombo-angiitis obliterans" (3). During the past 22 years, Silbert has studied in the Peripheral Vascular Disease Clinic at The Mount Sinai Hospital and in his private practice over 1400 patients suffering from thrombo-angiitis obliterans. In this group only two patients were encountered in whom both thrombo-angiitis obliterans and diabetes were present (4).

On the contrary, arteriosclerosis and diabetes are commonly seen in the same individual. There has been no agreement on the explanation for this frequent association. The high blood cholesterol usually found in diabetic patients has been regarded by many investigations as the important factor favoring the early onset of diabetes. However, Moscheowitz believes that in the adult form of diabetes, arteriosclerosis is the cause rather than the result of the disease. He states that it acts by causing insufficiency of the islands of Langerhans through a mechanism of arterio-capillary fibrosis (5). Most observers do not agree with this view of the pathogenesis.

The presence of arteriosclerosis in the patient with diabetes frequently gives rise to symptoms of impaired circulation in the lower extremities. When peripheral vascular disease is found in a diabetic, it is usually safe to assume that it is arteriosclerotic in nature. Thrombo-angiitis obliterans has some distinguishing characteristics, but often it can be differentiated from arteriosclerotic peripheral vascular disease only by exclusion. It is a fair assumption that when there is evidence of generalized arteriosclerosis in the body, the peripheral vascular disease in the extremities is on the same etiological basis. Not only must arteriosclerosis be absent from the peripheral vessels, but it must be searched for, and excluded in other parts of the body before a diagnosis of thrombo-angiitis obliterans can be made. Thus, the presence of coronary sclerosis, by inference, would imply that the peripheral vessels were sclerotic, even though x-rays of the lower extremities failed to reveal evidence of calcification of the vessels. The following table, based upon a chart published in 1935 by Silbert (6) lists the criteria for the differential diagnosis between thrombo-angiitis obliterans and arteriosclerotic peripheral vascular disease (Table I).

Before the diagnosis of thrombo-angiitis obliterans and diabetes in the same patient can be accepted, it is necessary that the following two criteria are present. First, the vascular disease should precede the onset of the metabolic disease by several years, and second, the vascular disease should occur before the age of forty.

Several authors have reported the association of thrombo-angiitis obliterans and diabetes in a small number of patients. In our opinion none of these reports can be accepted because all of the patients failed to fulfill one or both of the above criteria. In most of the cases, the age of onset was over forty.

TABLE I

|                                  | THROMBO-ANGIITIS OBLIT. | ARTERIOSCLEROTIC PERIPH. VASC. DISEASE |
|----------------------------------|-------------------------|--|
| Intermittent claudication.....   | Present                 | Present                                |
| Symptoms of coronary sclerosis.. | Absent                  | May be present                         |
| Age of onset.....                | Under 45                | Often over 45                          |
| History of smoking.....          | Always                  | Not always                             |
| Pulses.....                      | Absent                  | Absent                                 |
| Involvement of upper extremities | Frequent                | Rare                                   |
| Blood pressure.....              | Often low               | Frequently elevated                    |
| Fundi.....                       | Negative                | May have sclerotic vessels             |
| Hair.....                        | Normal                  | Frequently gray                        |
| Arcus senilis.....               | Absent                  | Frequently present                     |
| X-ray of extremities.....        | No calcification        | Calcification often present            |
| Electrocardiogram.....           | Negative                | May show myocardial damage             |
| Urine.....                       | Usually negative        | Frequently albumin and/or glycosuria   |
| Red blood cell count.....        | Often above normal      | Usually normal                         |
| Hemoglobin.....                  | Often above normal      | Usually normal                         |
| Blood volume.....                | Often below normal      | Usually normal                         |
| Basal metabolism.....            | Usually low             | Usually normal                         |
| Prognosis.....                   | Relatively good         | Relatively poor                        |

Davidson's (7) patient was 65 years old, and Delbet's (8) patient was 61 years old at the time of the onset of the vascular disease. Of the cases reported by Adams (9), by Horton and Allen (10), and by Helm and Horton (11), ten cases in all, only one was less than forty at the time the vascular disease began. In this patient, who was 38, the onset of the vascular disease coincided with the onset of the diabetes. In a number of the remaining patients all of whom were above forty, calcification of the blood vessels was present. The case reported by Collens and Wilensky (12), had hypertension and calcified blood vessels.

The first patient presented here has been observed in the wards and clinics of The Mount Sinai Hospital since 1930. He has diabetes mellitus, and also presents all of the requirements for a typical case of thrombo-angiitis obliterans. In addition, careful search has revealed no evidence of arteriosclerotic involvement elsewhere.

## CASE REPORTS

*Case 1. History:* H. L. (Adm. #334613) now 45 years, was first seen by us 13 years ago when he was 32 years old. He is an American born Hebrew, and a chauffeur by occupation. At his first visit to the Peripheral Vascular Clinic of the Out-Patient Department, he complained of a painful ulcer on the left big toe. About two weeks later, he was admitted to a medical ward of the hospital because the ulceration was too extensive for out-patient treatment. In the hospital, the following history was elicited:

He first noted intermittent claudication at the age of 22 (making the total duration of his illness 23 years, at the present time).

For 6 years, he had noted intermittent, red, linear, tender swellings on the lower extremities—evidently recurring phlebitis migrans.

For 2 years, he had noted redness, swelling and pain in the toes of his left foot.

During the past 6 months, transient ulcers had appeared on the third, fourth and fifth toes of the left foot.

During the month prior to admission, the left big toe had become red, painful, swollen and progressively ulcerated.

He smoked about 20 cigarettes daily.

*Examination:* Patient was a tall thin individual. The eyes, including the retinal vessels were normal. The heart was not enlarged. The sounds were regular and of good quality, and there was a short systolic murmur at the apex. Electrocardiogram was reported to be normal. Both radial pulses were equal and apparently not sclerotic. Blood pressure was 120 systolic and 80 diastolic. The examination was negative otherwise, until the lower extremities were reached. Both femoral and both popliteal arteries pulsated normally. In the right foot, only the peroneal pulse could be felt, all the other arterial pulses being absent. In addition, the left foot was purplish-red, with an area of sloughing gangrene near the tip of the first toe, and with bluish discoloration of the two adjoining toes. The oscillometric readings were as follows: right calf—3.0, right ankle—2.0, left calf—2.5, left ankle—0.5.

*Laboratory data:* Hemoglobin was 84 per cent. The blood count including the differential count, and the bleeding time, the coagulation time and the sedimentation rate were all normal. The urine was examined repeatedly and reported normal. At no time was the presence of glycosuria noted. Blood urea and total proteins were normal. Both Wassermann and Kahn tests were negative. There is no record of the blood sugar at this time. The diagnosis made in the hospital was thrombo-angiitis obliterans with gangrene of the toe.

*Course:* Treatment consisted of 300 cubic centimeters of 5 per cent sodium chloride, injected intravenously, every other day, and sterile bland applications to the ulcer. In addition, smoking was stopped completely. His course was uneventful, except for a transient, superficial phlebitis of the left thigh. At the end of 5 weeks, he was discharged from the ward, and advised to remain in bed except when visiting the clinic. He was advised also to use crutches until the ulcer was healed completely, and above all, not to resume smoking.

Treatment thereafter was continued in the Peripheral Vascular Clinic of the Out-Patient Department of the hospital. He received intravenous injections of 5 per cent sodium chloride several times a week, the ulcer was treated with sterile bland dressings, and he was cautioned repeatedly about smoking. The ulcer was healed completely within six months, and several months later, he reported that he was able to walk six to eight blocks. Eighteen months after the onset of treatment, he stated that he was able to walk "indefinitely." His progress during the fourteen years that he has been under our observation and treatment is shown in Table II.

Glycosuria was noted, first in 1936, when routine urine examinations revealed, first 1 per cent, and later 2.5 per cent glucose. There was no change in the peripheral vascular disease insofar as could be determined by, his ability to walk, palpation of pulses or oscillometric

readings. However, two years later, he complained of loss of weight, and the urine was found to contain 10 per cent glucose. He was then referred to the Metabolism Clinic. A blood examination revealed that his blood glucose was 170 mg. per cent.

A diet of carbohydrate—150 grams, protein—70 grams, and fat—70 grams was ordered, together with 10 units of protamine zinc insulin. On this regime, his urine became negative and the blood glucose decreased to 125 mg. He has been followed in the Metabolism Clinic up to the present time. He maintains his weight on the above diet. Glycosuria is usually absent, although it has been found on several examinations, the highest reported being 1.9 per cent. The blood glucose has not been reported above 136 mg. per cent. The insulin dose was changed several times, varying from 10 to 30 units. His blood cholesterol was found to be 215 mg. per cent on one examination, and 220 mg. per cent on another examination. At the present time, the urine contains no glucose and the daily insulin dose is 20 units.

TABLE II

| DATE            | FUNCTION           | PULSES      |              |             |        |             |              |             |        | OSCILLOMETER |       |
|-----------------|--------------------|-------------|--------------|-------------|--------|-------------|--------------|-------------|--------|--------------|-------|
|                 |                    | Left Foot   |              |             |        | Right Foot  |              |             |        | Ankle        |       |
|                 |                    | Anter. tib. | Poster. tib. | Dorsal ped. | Peron. | Anter. tib. | Poster. tib. | Dorsal ped. | Peron. | Left         | Right |
| 1930.....       | In bed             | 0           | 0            | 0           | Open   | Open        | 0            | Open        | Open   | 1.5          | 2.0   |
| Sept. 1930..... | Ulcer              | 0           | 0            | 0           | Open   | 0           | 0            | Open        | Open   | 1.5          | 2.0   |
| April 1931..... | Uses crutches      | 0           | 0            | 0           | Open   | 0           | 0            | Open        | Open   | 1.5          | 4.0   |
| Feb. 1932.....  | Walks indefinitely | 0           | 0            | 0           | Open   | 0           | 0            | Open        | Open   | 2.5          | 3.5   |
| April 1934..... | Walks indefinitely | 0           | 0            | 0           | Open   | 0           | 0            | Open        | Open   | 3.0          | 4.0   |
| Dec. 1936.....  | Walks well         | 0           | 0            | 0           | Open   | 0           | 0            | Open        | Open   | 3.5          | 3.5   |
| Jan. 1939.....  | No note            | 0           | 0            | 0           | Open   | 0           | 0            | Open        | Open   | 3.5          | 4.0   |
| May 1942.....   | Walks any distance | 0           | 0            | 0           | Open   | 0           | 0            | Open        | Open   | 3.0          | 3.5   |
| Sept. 1944..... | Walks any distance | 0           | 0            | 0           | Open   | 0           | 0            | Open        | Open   | 3.0          | 3.0   |

For the past few years this patient has been employed full time as a bus driver. He is able to work and walk about as well as the average male of his age. He has not smoked for the past 14 years. The peripheral pulses which were open in 1930, namely, the left peroneal, and the right dorsalis pedis and the right peroneal remain open to this date. While no new pulsation has appeared in either foot, the oscillometric reading at each ankle has doubled during the 14 years of observation. He visits the vascular clinic about once a month, and the metabolism clinic about once in six weeks.

*Case 2. History:* M. G. (Adm. #3323021) a Russian born Jewish male who is now 51 years old, is the second patient in whom the rare association of diabetes mellitus and thrombo-angiitis obliterans has been found. He was admitted to The Mount Sinai Hospital in 1922, at which time he was 29 years old. He complained of a painful ulcer on the left great toe for the five weeks preceding his admission. He stated that he had been smoking about 15 cigarettes a day for a great many years.

*Examination:* The relevant findings upon physical examination were a discolored great toe (left) with a small ulcer on the inner aspect. On the left side, the popliteal, the posterior tibial, the anterior tibial and the dorsalis pedis arteries were closed. In the right foot, all the arteries were closed except the posterior tibial which could be palpated. The blood pressure was 120 systolic and 77 diastolic.



*Laboratory data:* Eight urine examinations were made. These were all negative for sugar, acetone and diacetic acid. Four blood sugar determinations were made. These were all within normal limits.

*Course:* The diagnosis was thrombo-angiitis obliterans. Treatment consisted in the injection of the left posterior tibial nerve with alcohol for the relief of pain. Three weeks after admission he was discharged with the notation that he was improved.

The following year, 1923, he was again admitted with the complaint that the pain in the left great toe had recurred during the preceding two weeks. The ulcer on this toe was still present. The treatment on this admission consisted of intravenous injections of 5 per cent sodium chloride in addition to bed rest and sedatives. After a period of three weeks he was discharged with the notation that the pain had disappeared completely and the ulcer had healed. For the next six months he was treated in the Out-Patient Department of the hospital and felt quite well.

However, the original ulcer recurred, and in addition, an ulcer developed on the third toe of the left foot. He was readmitted to the hospital on May 12, 1924, where a periarterial sympathectomy was performed. Sixteen days later, he was discharged "improved" and advised to continue treatment in the out-patient department.

TABLE III

| DATE                | FUNCTION | PULSES      |              |              |        |             |              |              |        | OSCILLOMETER |       |
|---------------------|----------|-------------|--------------|--------------|--------|-------------|--------------|--------------|--------|--------------|-------|
|                     |          | Left foot   |              |              |        | Right foot  |              |              |        | Ankle        |       |
|                     |          | Anter. tib. | Poster. tib. | Dorsal. ped. | Peron. | Anter. tib. | Poster. tib. | Dorsal. ped. | Peron. | Left         | Right |
| Feb. 5, 1935 . . .  | Good     | —           | —            | —            | —      | 0           | Open         | 0            | Open   | —            | 4.0   |
| Oct. 19, 1937 . . . | Good     | —           | —            | —            | —      | 0           | Open         | 0            | Open   | —            | 3.5   |
| Nov. 7, 1939 . . .  | Good     | —           | —            | —            | —      | 0           | Open         | 0            | Open   | —            | 4.0   |
| Dec. 2, 1941 . . .  | Good     | —           | —            | —            | —      | 0           | Open         | 0            | Open   | —            | 3.0   |
| Dec. 7, 1943 . . .  | Good     | —           | —            | —            | —      | 0           | Open         | 0            | Open   | —            | 2.5   |
| May 9, 1944 . . .   | Good     | —           | —            | —            | —      | 0           | Open         | 0            | Open   | —            | 2.5   |
| Nov. 5, 1944 . . .  | Good     | —           | —            | —            | —      | 0           | Open         | 0            | Open   | —            | 2.5   |

Within six weeks he was readmitted to the hospital, his fourth admission. In addition to the two ulcers, there was a painful swelling of the entire left foot. After an attempt at conservative treatment, a mid thigh amputation was performed. He made an uneventful recovery from the operation and was discharged from the hospital after a stay of about 35 days. The specimen was sectioned in the pathology laboratory and reported "thrombo-angiitis obliterans."

Thereafter, he was treated in the Out-Patient Department. He stopped smoking entirely and received intravenous injections of 5 per cent sodium chloride. There were no complaints referable to his peripheral vascular system. On July 13, 1926, a peroneal pulse appeared over the external malleolus of the remaining extremity. This was in addition to the posterior tibial pulse which was found on the first examination. The oscillometric readings on the right leg at this time were, calf—4.5, ankle—3.5. On April 15, 1931, about five years later, it was noted that the same two pulses were present and that the oscillometric reading at the ankle was 5.0. Repeated examinations during the ensuing years up to the present time revealed no change in his vascular status. He required no treatment during these years, coming to the clinic only for check-up examinations. He has been getting about fairly well on his artificial appliance (Table III).

Diabetes mellitus became evident in April 1943, when the urine was found to contain 2 per cent sugar. The blood sugar was reported 164 mg. per 100 cubic centimeters. He was

treated by diet alone, without insulin. The urine became sugar-free, and the blood sugar fell to 142 mg. within a short time.

#### DISCUSSION

In 1918, Willy Meyer and Adolph Bernhard (13) studied the glucose metabolism in a series of 15 patients suffering from thrombo-angiitis obliterans. In 11 of these cases the fasting blood sugar was normal. In 3 of the cases, the fasting blood sugar was between 120 and 140 mg. per cent and in one case it was 168 mg. per cent. Two hours after the ingestion of 100 grams of glucose, six of the fifteen cases had an elevated blood sugar, ranging from 138 to 215 mg. per cent. Curiously, the patient whose fasting blood sugar had been 168 mg. per cent was found to have only 126 mg. per cent two hours after the ingestion of the glucose. On the basis of these findings, Willy Meyer believed that thrombo-angiitis was a metabolic disease and proposed the name of "glycophilia" for it.

However, these findings have not been confirmed. On the contrary, Friedlander and Silbert (13), who studied a group of 53 thrombo-angiitis obliterans patients found the fasting blood sugar to be normal. Glucose tolerance tests on the patients "failed to show any striking abnormality." We were unable to find any other reports on the glucose metabolism in thrombo-angiitis obliterans in the literature. In view of these facts, Meyer's theory of disturbance of sugar metabolism can not be accepted.

There are several factors which both thrombo-angiitis obliterans and diabetes mellitus have in common, and it seems strange that the combination of the two diseases is so rare. Both disorders occur more frequently in Jews than in non-Jews. The blood cholesterol is frequently elevated in both diseases. Also, impotence is a frequent complaint, and obesity a frequent finding in both diseases. The rarity of association of thrombo-angiitis and diabetes despite these common factors suggests the possibility of an antagonism between the two disorders. However, nothing has been found as yet, to reveal any such antagonism.

Since thrombo-angiitis obliterans is known to involve the abdominal blood vessels in advanced cases of the disease, the two cases reported here might represent such involvement of the pancreatic vessels. However, this appears to be unlikely for in neither case was the peripheral arterial involvement very extensive. Moreover, the fact that the peripheral involvement in both cases had been arrested for many years prior to the onset of the diabetes speaks strongly against the possibility of disease of the pancreatic vessels. It is characteristic of thrombo-angiitis obliterans to involve the distal blood vessels of the extremity first. The disease then spreads up the leg and thigh if not arrested, and the abdominal vessels are usually the last to be involved. In his book, Buerger (1) cites necropsy reports of several cases with involvement of intra-abdominal vessels. All of these cases had extensive involvement of the peripheral vessels, necessitating the amputation of one or more extremities. Also, diabetes was not reported present in any of the cases cited. The evidence

is therefore insufficient to warrant the conclusion that the pancreatic vessels were involved by thrombo-angiitis obliterans in the two cases reported here.

#### SUMMARY

Two cases are reported in which both thrombo-angiitis obliterans and diabetes mellitus are present.

Neither causal relationship nor antagonism has been found to explain the rare association of these two diseases in the same individual.

#### REFERENCES

1. BUEGER, L.: *The Circulatory Disturbances of the Extremities*. Philadelphia, W. B. Saunders Co., 1924.
2. HOMANS, J.: *Circulatory Diseases of the Extremities*. New York, The Macmillan Company, 1939.
3. MCKITTRICK, L. S.: Indications for amputation in progressive arterial obliteration of lower extremities. *Ann. Surg.*, 102: 342, 1935.
4. Personal Communication.
5. MOSCHCOWITZ, E.: *Vascular Sclerosis*. New York, Oxford University Press, 1942.
6. SILBERT, S.: Thrombo-angiitis obliterans. Treatment of 524 cases by repeated intravenous injections of hypertonic salt solutions. Ten years experience. *Surg., Gynec. & Obst.*, 61: 214, 1935.
7. DAVIDSON, H. S.: Thrombo-angiitis obliterans and diabetes, *J. M. Soc. New Jersey*, 28: 570, 1931.
8. DELBET, P.: Gangrene Seche du Membre Inferieur Chez un Malade Diabetique et Syphilitique. A propos de la Maladie de Buerger, *Rev. gen. de clin. et de therap.*, 12: 659, 1927.
9. ADAMS, S. F.: A case of diabetes mellitus with thrombo-angiitis obliterans. *Clin. N. Amer.*, 581, 1930.
10. HORTON, B. T., AND ALLAN, F. N.: Thrombo-angiitis obliterans with diabetes. *Ann. Int. Med.*, 7: 799, 1934.
11. HELM, S., AND HORTON, B. T.: Thrombo-angiitis obliterans associated with diabetes mellitus. *Ann. Int. Med.*, 12: 1493, 1939.
12. COLLENS, W. S., AND WILENSKY, N. D.: Thrombo-angiitis obliterans in diabetic. *Am. Heart J.*, 17: 624, 1939.
13. MEYER, W.: Etiology of thrombo-angiitis obliterans. *J. A. M. A.*, 71: 1268, 1918.
14. FRIEDLANDER AND SILBERT: Studies in thrombo-angiitis obliterans. *Arch. Int. Med.*, 1931.

## LIFE'S LATER YEARS

### STUDIES IN THE MEDICAL HISTORY OF OLD AGE

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#### PART 7<sup>1</sup>

#### THE MEDIEVAL PERIOD (1096-1438)

*"But amonge all other thynges there is nothyng, the which so strongly doth cause a man to look oldely, as feare and desperacioun. For because in that passion and effectyon, all the naturall hete of the body doth resort inwarde and forsaketh the outward partes, and ye most chefully, when the manes complexyon is disposed to the same, and that is the cause that many beyng toste, turmoyled, and vexed with this worldly stormes so vaynly, theyr heer waxe hore, or whyte."*

*Arnold of Villanova—The Conservation of Youth and Defense of Age.  
(Drummond's translation—1544 A. D.)*

The social and political chaos, which preceded and followed the fall of the Roman Empire, brought about spiritual confusion, disillusionment, and hopelessness in the minds of men. To the suffering multitudes, as well as to their rulers, the Christian Church brought a message of comfort, and the hope of a better life in the hereafter for the faithful. Its preachment of sympathy for the sufferer and of care for the poor, the sick, and the old, led to the establishment of ecclesiastical hospitals and nursing orders. Medicine during the Dark Ages in Western Europe found its only home in the monasteries where the works of the great Greeks and Romans were copied and preserved; but rigid adherence to accepted rules and blind respect for authority suppressed all striving for new knowledge.

The supercilious attitude of the church toward the human body was officially expressed in the book of Pope Innocent III, "*De Contemptu Mundi sive de Miseria Humanae Conditionis*." Chapter X of the treatise treats of the brevity of life, Chapters XI and XII take title from Horace's opening line, "*De incommodis senectutis*" (1). The description of old age enlarges that of Horace in stating that the aged are "easily provoked, stingy, avaricious, sullen and quarrelsome, quick to talk, slow to hear, but not slow in wrath, praising former times, despising moderns, censuring the present, commending the past." The moral of this discourse is, "Young man, be not proud in the presence of a decaying old man; he once was that which you are, he now is that which you in turn will be." Coffman points out how this epitomizes the change from Augustan paganism

<sup>1</sup> This is the seventh in a series of articles dealing with the Medical History of Old Age. Upon completion of their publication, the installments will be collected and reprinted in a single volume, constituting one of the Monographs of The Mount Sinai Hospital Press.—Ed.

to medieval asceticism and the supplanting of the *carpe diem* of Roman stoicism by the *memento mori* theme of medieval Christianity (2). Another feature of Church policy inimical to medicine was a series of edicts listed by Garrison (3), whose object was primarily aimed at malpractice by monks, but had the general effect of not only discouraging clerical medicine, but also of placing their odium on the whole medical profession.

The Medical School of Salerno, first of its kind in Western Europe flourished in the eleventh and twelfth centuries. If not founded by the clergy it was at

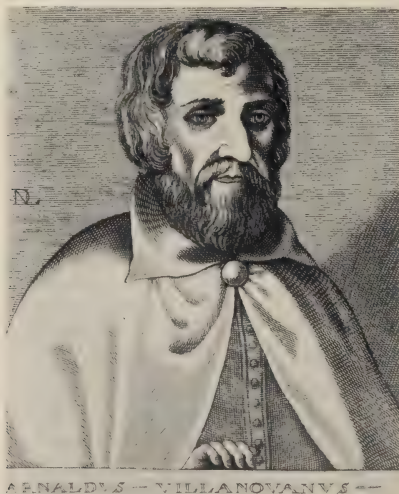


FIG. 1. Arnold of Villanova (1238-1311). (Reproduced from print in the collection of the Home for Aged and Infirm Hebrews, N. Y.)

least under church auspices. This institution of learning gradually came to form the focal point of Monastic, Greek, Jewish and Arabic medical learning, and exerted a wide influence in Italy and other parts of Western Europe. The Salernitan masters covered many fields of medicine in their writing, of which the most famous is the *Regimen (Sanitatis) Salernitanum* or *Flos Medicinæ* (1260-1300), a popular work in poetic form, written for the King of England, the purpose of which was, in the words of the subtitle of the English translation of Sir John Harington (4), "the perfect preserving of the body of Man in continual health."

This famous medical work, known to have had a wide currency in manuscript form and to have gone through some 200 editions after the invention of printing,



follows the precepts of healthful living as laid down by Avicenna, Maimonides and other Arab writers, quoted in the previous sections. In discussing the various herbs and their properties, the unknown author exclaims:—

*"But who can write thy worth (O sovereigne Sage!)  
Some aske how man can die, where thou dost grow;  
Oh that there was a medicine curing age,  
Death comes at last, though death comes ne're so slow."*

The importance of age in the indications for phlebotomy is twice stressed.

*"Of seventy from seventeene, if bloud abound,  
The opening of a veine is healthfull found."*

*"Too old, too young, both letting bloud displeases,  
By years and sicknesse make your computation."*

A famous commentary on this poem was written by Arnold of Villanova (1238–1311), the distinguished Spaniard, whose fame spread far and wide as the result of his sound medical ability, his books on medical subjects and his chemical investigations. In his famous "Parables of the Healing Art", he discusses the value of drug therapy and inveighs against the indiscriminate use of drugs in a manner more modern than medieval.

*"A conscientious and thoughtful physician will never hurry with drug therapy, when necessity does not force him since even weakly acting remedies may be harmful, if the body has no need of them.*

*With children and older people one must hesitate before administering drug remedies, even in youth the frequent taking of drugs is of doubtful value.*

*People who frequently take drugs in youth, will complain early of the troubles of old age."* (5)

At the request of King James of Spain, Arnold published in 1290 a treatise entitled, "*De Conservatio Juventutis et Retardatione Senectutis*" (6). The English translation by Dr. Drummond did not appear until 1544, over 250 years later and was called "The Conservation of Youth and the Defense of Age" (7). Arnold's theory of old age was based on the old Galenical pathology, as set forth by the Arabian school. Health depends on the equilibrium between the four temperaments, hot, cold, wet and dry, and the four humors, blood, phlegm, yellow bile, black bile. In old age cold and dry humors predominate and deplete the body. To overcome this the warm and moist humors must be stimulated. Arnold presents a regimen for each humor and temperament, and attention to these prevents old age. In general, his advice is eminently rational. Moderation in all things is advised. Life is to be regularly divided between moderate exercise, physical repose, waking and sleeping, mental work and some kind of amusement. Intellectual diversions are stressed, such as music, story-telling, theaters, travel-

ling. He advocates well ventilated homes, proper clothing and frequent bathing. His drug therapy, largely vegetable remedies and medicinal wines, is secondary to hygienic measures of a general nature.

Of old folys that is to say the longer they  
lyue the more they ar gyuen to foly.



Howebeit I stoup, and fast declyne  
Dayly to my graue, and sepulture  
And though my lyfe fast do enclyne  
To pay the trybute of nature  
Yet styll remayne I and endure  
In my olde synnes, and them nat hate  
Nought yonge, wors olde, suche is my state.

FIG. 2. This wood-cut showing an old man with one foot actually in the grave is taken from a contemporary English translation of Sebastian Brant's famous satirical and didactic poem "Das Narrenschiff" (The Ship of Fools) published in 1494.

In Arnold of Villanova we see an inquiring mind, a keen observer, and a practical physician, who, while still imbued with Arabian theory, was not afraid to set forth his own views and to defend them. Something of this same spirit of independence stirred Maimonides when he ventured to criticize Galen, and is indeed, an outstanding characteristic of Roger Bacon (c. 1214-c. 1294), largely unappreciated in his own day, but described by Garrison as "comparative philol-

ogist, mathematician, astronomer, physicist, physical geographer, chemist and physician." His chief contribution to science was as a practical experimenter whereby he anticipated many modern inventions. He is important in this narrative of the development of our knowledge of geriatrics for his book on old age, and his contribution to the development of eye-glasses.

*"Very rarely does it happen that anyone pays sufficient heed to the rule of health. No one does in his youth, but sometimes one in 3,000 thinks of these matters, when he is old and approaching death, but he cannot apply a remedy because of his weakened powers and lack of experience. Therefore fathers are weakened and beget weak sons, then by neglect of rules of health, the sons weaken themselves and thus the son's son has a doubly weak constitution, the shortening of life of this kind is accidental and therefore a subject to remedy, if from birth a man followed a proper rule of life he would reach the limit set by God and nature."* (Opus Majus) (8)

*"If a man looks at letters or other small objects through the medium of a crystal or a glass or of some other transparent body placed above the letters, and it is the smaller part of a sphere whose convexity is towards the eye and the eye is in the air, he will see the letters much better and they will appear larger to him. For in accordance with the truth—all conditions are favourable for magnification—Therefore this instrument is useful to the aged and to those with weak eyes. For they can see the letter, no matter how small, sufficiently enlarged."*

(Opus Majus, Burke's translation, p. 574.) (9)

Roger Bacon is celebrated *inter alia* for the invention of gunpowder, the result of his great interest in alchemy. This primitive chemistry, had, as the name implies, its origin in ancient Egypt, (Land of Kemi, Black Land, hence also the term Black Art, meaning alchemy or magic), and has its theoretical foundation, according to Davis, (11) the great historian of chemistry, in the doctrine of the two contraries. This concept also appeared in China (12) in the third and fourth century, B.C., in a state of maturity that leads Davis to conclude that it was probably an importation into that country.

"The positive and active principle was identified with the sun, the male, dry, light and fiery; the negative and passive principle with the moon, female, moist, heavy and cold. When men became interested in the chemical properties of metals, they of course supposed them to be the result of the confluence of the two groups of opposite forces and qualities, or in other words, of the combination of the two contrary principles. Zozimos and the Alexandrians of about the third century A.D. called the fiery principle Sulphur and the negative principle Mercury, and supposed all metals to be combinations of the Sulphur and Mercury principles. Jahir taught the doctrine in the eighth century. Albertus Magnus and Roger Bacon continued it. Becker in the seventeenth century gave the name of *terra pinguis* (fat earth) to the sulphur principle. Stahl shortly afterwards renamed it phlogiston (the fiery entity) and the doctrine dominated

chemistry until the time of Lavoisier. Alchemy, understood as the pursuit of transmutation and the elixir, does not seem to have been practised by the Alexandrians but first appeared among the Arabs of about the eighth century" (13). The alchemists of that time believed that if the two contraries could be made to unite or combine, that the Real Gold, the Philosopher's Stone, the Pill of Immortality and the Grand Elixir could be produced. This brief outline helps us to comprehend how the research activities of a group of medieval thinkers in their efforts to solve the riddle of life and death, laid the foundations for a modern science, full of rich promise today for an eventual clarification of the same problem.

In his book "The Care of Old Age and Preservation of Youth," Bacon attempts to convey to the lay reader the knowledge necessary to attain the ideal mentioned in the quotation from his *Opus Majus*. This geriatric work, known only in Latin manuscript for centuries, finally was translated by Dr. Richard Browne of London in 1683 (10). Bacon depended largely on the Arabs for his opinions and quoted constantly from Isaac Bemiramis, Haly Abbas, Avicenna, Averroes, Rhazes, and Johannes Damascenus, as well as Aristotle, Pliny and Galen. The outline of the book as well as its substance depends largely on the Moslem prototypes. The infirmities of old age, their nature and prevention, proper regimen to be followed by the old, all these topics are covered, together with chapters on diet and wines. The final paragraph of the final chapter furnishes an excellent summary of the spirit as well as the content of the entire work.

*"Whence in conclusion it is made manifest, that Mirth, Singing, Looking on Humane Beauty and Comeliness, Spices, Electuaries, warm Water, Bathings, some things lying in the Bowels of the Sea, some living in the Air, others taken from the noble Animal, well tempered and prepared, and many more such things are Remedies whereby the Accidents of Age in Young Men, the Infirmities of Old Age in Old Men, the Weakness and Diseases of Decrepit Age in very Old Age, may be restrained, retarded and driven away."*

While the scientist of the Middle Ages worked with crucible and alembic, the people, both rich and poor, found solace not only in the religion that played so large and dominating a role in their lives, but also in romantic tales of high adventure, in part stimulated by the Crusades. While many stories had to do with love and battle, some told of the quest for the fountain of Juventa, celebrated in Greek folklore as the spring formed in the metamorphosis of the nymph Juventa by Jupiter, and capable of rejuvenating those who bathed in it (14). Many of these medieval tales are based on the life of Alexander the Great, whose adventures formed part of the literature of all countries. Poems of the Middle Ages, French, German and Italian, are consecrated to the hero and in each of these is found the discovery of the fountain. The oldest Roman d'Alexandre is the work of Lambert-li-Cora de Chatendun and Alexandre de Bernay in 1184 A.D.

The famous Sir John Mandeville discovered the place in 1372 and located it in a narrow valley between a bare rock and a verdant hill near the city of Polo-



FIG. 3. The Fountain of Juventa, by Lucas Cranach the Elder (1472-1553).



nibes (?) and described it as follows:—"It has the odor and taste of spices, and at each hour of the day exhales new perfumes, and whoever drinks this fountain is cured of every malady he has, and seems always to be young; all call it the Fountain of Juventa." The vain quest of Ponce de Leon in Florida is well known, and in many of the early tales of discoveries in the New World, the fountain was definitely located. De Soto is said to have had it as an object of his wide travels.

In a strange parallel the mystic religion of the epoch took up the same idea in attributing to the blood of the Saviour the merits of the marvelous water. This is explained in the Legend of the Holy Grail of Robert de Baron written toward the end of the twelfth century. The Grail is the cup used at the Last Supper by Jesus and his disciples. In it Joseph of Arimathea collected the blood flowing from the wounds of the Saviour. Put into prison, Christ appeared to him and said, "I shall not take you with me; stay here until they think you are dead, but have no fear; you shall suffer no pain, and thou shalt not die." The divine blood thus became the fount of immortality and inspired many of the artists of the Middle Ages. Frescoes, engravings, tapestries and paintings are based on the theme of the pagan fount and its religious counterpart. Of them all, the most famous is the painting of Lucas Cranach, the Elder, now in the Berlin Museum, executed in 1546, and showing in lively fashion the magical transformation of weak old ladies into gay and flirtatious young women. Curiously enough, the only men shown are those waiting to receive the rejuvenated females (Fig. 3).

In sharp contrast with Arabist medical lore, the efforts of alchemists, and the romantic strivings of the medieval poets and painters, stands the marvelous insight and objectivity of Geoffrey Chaucer (1340-1400) whose Canterbury Tales give an intimate and revealing picture of the life of his time. Coffman has traced Horace's lines on old age through fourteen centuries to their enriched reappearance in the Reeve's Prologue. Chaucer's use of a classic inspiration for his own original purpose is a characteristic fore-runner of the spirit of the Renaissance, when, starting afresh with the originals of the classics, men once more began to think as Hippocrates had done, 1800 years earlier.

*"But ik am old, me list not pley for age;  
 Gras-time is doon, my fodder is now forage,  
 This whyte top wryteth myne olde yeres,  
 Myn herte is al-so mowled (a) as myne heres,  
 But—if I fare as dooth an open-ers; (b)  
 That ilke fruit is ever long the wers,  
 Til it be roten in mullok (c) or in stree (d).  
 We olde men, I drede, so fare we;  
 Til we be roten, can we nat be rype;  
 We hoppen ay, whyl that the world wol pype.  
 For in oure wil ther stiketh ever a nayl,  
 To have an hoor heed and a grene tayl,  
 As hath a leek; for thogh our might be goon,*

Our wil desireth folie ever in oon.  
 For whan we may nat doon, than wol we speke;  
 Yet in oure asshen olde is fyr y-reke (e).  
 Foure gledes (f) han we, whiche I shal devyse,  
 Avaunting, lying, anger, coveityse;  
 Thise foure sparkles longen un-to elde.  
 Oure olde lemes mowe wel been unwelde (g).  
 But wil ne shal nat faillen, that is sooth.  
 And yet ik have alwey a coltes tooth,  
 As many a yeer as it is passed henne,  
 Sin that my tappe of lyf bigan to renne.  
 For sikerly, whan I was bore, anon  
 Deeth drogh the tappe of lyf and leet it gon;  
 And ever sith hath so the tappe y-ronne,  
 Til that almost al empty is the tonne.  
 The stream of lyf now droppeth on the chimbe; (h)  
 The sely (i) tonge may wel ringe and chime  
 Of wrecchednesse that passed is ful yore;  
 With olde folk, seve dotage, is namore." (15)

- |                  |                       |
|------------------|-----------------------|
| (a) grown mouldy | (f) burning coal      |
| (b) medlars      | (g) unwieldy          |
| (c) rubbish      | (h) rim of the barrel |
| (d) straw        | (i) innocent          |
| (e) spread about |                       |

## REFERENCES

- (1) COFFMAN, G. R.: Old Age from Horace to Chaucer: Some Literary Affinities and Adventure of an Idea. *Speculum*, 9: 249, 1934. This account of Pope Innocent III is based on Coffman's essay.
- (2) For a scholarly treatment of the *memento mori* theme in medieval life, see F. Parkes Weber, *Aspects of Death and Correlated Aspects of Life in Art, Epigram and Poetry*, 3rd ed., New York, P. B. Hoeber, 1920.
- (3) GARRISON, F. H.: *History of Medicine*, ed. 4, Philadelphia, Saunders, p. 168, 1929.
- (4) *The School of Salernum, Regimen Sanitatis Salernitanum, The English Version*, by Sir John Harington, New York, P. B. Hoeber, 1920. All quotations in the text are from this translation.
- (5) The Second Doctrine-Aphorisms 11, 12, 13; translated from "Des Meisters Arnold von Villanova, Parabel der Heilkunst, aus dem lateinischen uebersetzt, erlaert und eingeleit" , Paul Diepgen, *Klassiker der Medizin*, Leipzig, 1922.
- (6) Contained in *Arnoldus de Villa Nova, Opera omnia*, Basiliae, Conrad Waldkirch, 1585, (Streeter Collection, New York Academy of Medicine).
- (7) *The Conservation of Youth and the Defense of Old Age* (1290); *Arnoldus Villanova* (d. 1311), trans. by Dr. Jonas Drummond, A. D. 1544, with additions from the *Breviarium of Arnoldus*, edited by C. L. Dana, The Elm Tree Press, Woodstock, Vt. 1922. The writer is indebted to Dr. Dana's excellent introduction.
- (8) WOODRUFF, E. WINTHROP: *Roger Bacon, A Biography*, London, James Clarke & Co., 1938, p. 111.
- (9) *Ibid*, p. 142. For the early history of eye-glasses, the development of which has meant so much for the comfort and happiness of the old, see Garrison's full account, *op. cit.* p. 184 et seq.

- (10) BACON, ROGER, *The Cure of Old Age and Preservation of Youth*, translated out of the Latin, with annotations and an account of life and writings, by Richard Browne; London, T. Flesher, 1683. (With this is bound, Madeira Arraiz, *De Arbor Vitae*, or a physical account of the Tree of Life.).
- (11) DAVIS, T. L.: *Pictorial Representations of Alchemical Theory*, *Isis*, 28: 75, 1938; see also *Problems of the Origin of Alchemy*, *Scientific Monthly*, 43: 551, 1936.
- (12) WILSON, W. J.: *Alchemy in China*, *Ciba Symposia*, 217, 1940, with an extensive bibliography.
- (13) DAVIS, T. L.: *Loc. cit.*
- (14) MASSON, L.: *La Fontaine de Jouvence*, *Aesculape*, 27: 244, 1937, and 28: 16, 1938. An excellent account of the legend in many countries with splendid illustrations.
- (15) From the Reeve's Prologue, *Canterbury Tales*, Geoffrey Chaucer, with introduction by T. R. Lounsbury, New York, T. Y. Crowell & Co., 1903. Decidedly worthy of re-reading at this point is Chaucer's keen picture of the "Doctour of Physik", whose education and personal peculiarities are particularly well described.

## ABSTRACTS

### AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Angina Pectoris and the Syndrome of Peptic Ulcer.* H. LEVY AND E. P. BOAS. Arch. Int. Med., 71: 301, March, 1943.

The symptoms of peptic ulcer and anginal symptoms may occur suddenly and simultaneously. Acute peptic ulcer may be associated with coronary thrombosis. Repeated attacks of angina pectoris at rest, finally eventuating in coronary thrombosis, may occur at the hours characteristic of pain from ulcer. When symptoms of angina pectoris and peptic ulcer coexist, successful treatment for symptoms of ulcer may cause remission of the anginal syndrome. Epigastric localization of anginal pain may be conditioned by a preexisting peptic ulcer. It is suggested that neurogenic mechanisms mediated by the vagus nerve are concerned in these associations.

*Dynamics of Intracapsular Cataract Extraction; Experimental Studies with Reference to the Suspensory Ligament, Hannover's Canal and Petit's Space.* J. GOLDSMITH. Arch. Ophth., 29: 380, March, 1943.

A new theory (colloidal) is propounded for the formation of cataracts. The zonular fibers on the orbiculus ciliaris are transformed into a continuous membrane by an inter-fibrillar cement substance (an original observation). A complete study was made with the corneal microscope of the internal and external dynamics of the intracapsular cataract extraction on fresh human eyes. The gross and microscopic anatomy of the anterior segment of the human eye is described. Radiographic and anatomic proof is offered for the existence of Hannover's Canal and Petit's Space as separate and independent chambers. The hyaloid is shown to be entirely independent of the suspensory ligament anatomically, embryologically, radiographically, and histochemically. The experiments demonstrate that the intracapsular cataract extraction can be undertaken in a great number of cases with a minimal amount of trauma.

*Paresis of Accommodation following Sulfadiazine Therapy.* J. LAVAL. Am. J. Ophth., 26: 303, March, 1943.

A young college student was given sulfadiazine over a period of five days during which time she ingested  $11\frac{1}{2}$  grams (173 grains) for influenzal rhinitis and pharyngitis. Two weeks later when she returned to school she noticed that it was quite difficult to read. Examination three months later revealed an accommodative power which was five diopters less than the average for her age. By prescribing glasses to correct her weakness of accommodation, the symptoms were alleviated and complete comfort was obtained.

*Lipid Nephrosis. Observations Over a Period of Twenty Years.* H. SCHWARTZ, J. L. KOHN AND S. B. WEINER. Am. J. Dis. Child., 65: 355, March, 1943.

A diagnosis of lipid nephrosis was made in forty children, admitted to The Mount Sinai Hospital, over a period of twenty years. Twenty-two of the patients are known to have died. Eight patients were followed for seven to twenty years. Four of these children now have hypertension and increased urinary sediment counts (Addis). Two others have increased urinary sediment counts only.

The temporary beneficial effect of an acute infection, such as measles, during the edematous phase, is discussed. The histologic changes in twelve necropsies is described; three of these cases had been ill from two to four years. The remainder for lesser periods. One could not predict from the clinical course the pathologic changes in the kidneys.

It is concluded, therefore, that most children with the classic clinical picture of lipid nephrosis have a glomerular involvement but perhaps in a different form from that seen in chronic or subacute glomerular nephritis.

*Treatment of tuberculosis of the oral cavity by carbon dioxide snow.* J. BERBERICH. Am. Rev. Tuberc., 47: 3, 290, March, 1943.

Carbon dioxide snow treatment was successfully applied in more than 200 cases of progressive tuberculous ulcers, tuberculous granulations and granulomata of the mouth, pharynx and larynx. Proliferative forms of tuberculosis react to this treatment only after a curettage has been performed. This treatment is painless and no disadvantages are observed. After an interval of two weeks the procedure is repeated and perhaps after another two weeks' interval, it may be repeated again. Two freezing applications are usually sufficient. The treated parts become clean very quickly, fresh granulations appear and after two weeks a smooth, fine scar develops. In addition, the inhalation of lime water (calcium hydroxide) is highly recommended in cases of ulceration with pain and difficulty on swallowing; the pains are quickly relieved.

*The Use of Detergents in the Cleansing and Local Treatment of Burns.* N. ROSENBERG. Surgery, 13: 3, 385, March, 1943.

According to Rosenberg, most workers are of the opinion that vigorous cleansing methods have no place in the preliminary treatment of burns because (a) anesthesia is required, (b) shock is thereby increased and (c) injury to remaining healthy tissue results. In many burns the tanning or coagulation method of local treatment seems to possess advantages, but infection arising from beneath the eschar speaks for the inadequacy of preliminary procedures. Certain of the synthetic detergents, employed in one of several combinations, act as cleansing agents in the local treatment of burns. Their unique properties which make them superior to other cleansing agents are (a) their ability to penetrate and "solubilize" substances such as greases, oils and fats as well as particulate matter, (b) their lack of irritating or tissue damaging properties, (c) their antiseptic nature and (d) the fact that after all greases, including the normal skin oils are removed, the subsequent take of dye or tanning agent is rendered easier and a proper eschar is more readily formed. In clinical tests with a number of detergent mixtures, performed both on controls with normal, intact skin and on 25 patients with relatively mild second degree burns, the properties listed were substantiated. More than three fourths of the burns when first observed in the emergency service of a metropolitan hospital were covered with grease, oil, fats or ointments. Burns covered with grease and oil, the result of military engagements, represent a problem in which the application of these new cleansing agents may be of specific benefit.

*The Indications for Jejunal Alimentation in the Surgery of Peptic Ulcer.* R. COLP AND L. J. DRUCKERMAN. Ann. Surg., 117: 3, 387, March, 1943.

The authors describe their experience with jejunostomy in a series of 51 patients suffering from recurrent chronic peptic ulcer. It was used as a preliminary, palliative, complementary and supplementary measure in the surgery of gastroduodenal ulceration. The technique of jejunostomy and jejunal alimentation is discussed. The indications and clinical applications are fully described as well as the evaluation of results.

*Hemangiopericytoma of the Omentum.* A. P. STOUT AND C. CASSEL. Surgery, 13: 578, April, 1943.

The case reported is one of a rare form of vascular tumor occurring in the omentum where tumors of a similar nature have not been previously described. The patient, aged



92, died of unrelated causes, having had a symptomless right para-umbilical mass, the size of a large kidney, for about sixty years. The tumor was composed of capillaries surrounded by cells believed to be proliferated Zimmermann's pericytes. These cells are normally found wrapped about capillaries and have contractile properties which, it is supposed, serve to narrow the calibre of the capillary lumen. The epithelioid cells of the glomus tumor are also pericytes.

*Chronic Partial Intestinal Obstruction due to Intussusception of an Appendix Epiploica.*

M. S. HARTE. Surgery, 13: 4, 555, April, 1943.

A case history is presented of a patient suffering from chronic partial intestinal obstruction caused by the intussusception of an epiploic appendix into the sigmoid which clinically was indistinguishable from an obstructing neoplasm. The author discusses the possible causes of this unusual condition.

*Erythema Infectiosum.* L. CHARGIN, N. SOBEL, AND H. GOLDSTEIN. Arch. Dermat. & Syph., 47: 467, April, 1943.

The authors report an outbreak of erythema infectiosum in a New York City orphanage in which 80 of 137 children housed in the institution when attacked. There were 80 primary attacks and 90 relapses. Girls were more predisposed to the disease than boys. In 64 per cent of the children the eruption was limited to the face, in 2 per cent to the body and in 33 per cent, the face and body. Infants and children between 1 and 4 years appeared to be immune. Extensive laboratory and epidemiologic studies failed to throw any light on the causation. Not a single case occurred in the public school attended by the children. The disease is apparently not transmitted by carriers. The incubation period is from 1 to 12 days. The facial eruption is characteristic and offers no diagnostic difficulties.

*Histaminase in the Treatment of Allergy in Children.* M. M. PESHKIN, H. G. RAPAPORT,

W. MESSER, I. FEUER, A. SICULAR, AND A. BERGER. J. Pediat., 22: 4, 426, April, 1943.

Forty-eight allergic children between ages of 3 and 16 years, suffering with various allergic disorders were given orally 50 units of histaminase daily for 2 to 20 weeks, or an average of 9 weeks per patient. Histaminase proved ineffectual as a prophylactic, phylactic or adjunctive therapeutic agent in all children treated.

*Hypertension in People over Forty.* A. M. MASTER, S. DACK, AND H. H. MARKS. J. A.

M. A., 121: 16, 1253, April, 1943.

The incidence of hypertension in persons over 40 has become increasingly important because of the greater number reaching this age. The authors surveyed 15,000 people representing a cross section of the population in middle and later life. In each decade from the 5th to the 9th, a large proportion of persons were found to be hypertensive. This was true particularly of systolic hypertension. Among men a majority were hypertensive beginning with the age of 60 for most of the limits and among women this occurred in some instances as early as the age of 50. It was found that regardless of the classification, the incidence of hypertension rose with each decade of life up to the 8th decade and in the case of systolic hypertension up to the 9th decade. The incidence of hypertension was higher in women and arose precipitously between 40 to 60 years of age, faster than in men. Systolic hypertension increased more rapidly than diastolic hypertension, resulting in increased pulse pressure with age. The presence of hypertension at the age of 40 and over is so common that a mild degree and perhaps a "moderate" degree can no longer be considered abnormal. Limitation of normal blood pressure at these ages should, therefore, be raised.

*Grenz Rays in their Application to Periodontal Disease.* R. H. BRODSKY. J. Am. Dent. A.,

30: 560, April, 1943.

A new and successful therapy in the treatment of periodontal lesions has been introduced by the author and used for more than seven years. Grenz radiation is applied directly to

the gingival tissue in addition to the usual conservative methods of therapy for the so-called pyorrhoeal and associated conditions. The Grenz ray, discovered by Dr. Gustave Bucky, lies in the wave length about half way between the ultra-violet and the x-rays. It has been used extensively in Europe for certain conditions, particularly dermatologic and endocrine, and had been conclusively demonstrated to be perfectly safe in doses much greater than are employed in the treatment of diseases of the gums. For mucous membrane therapy, the x-rays are too hard and too penetrative, while the ultra-violet rays are entirely too shallow. The Grenz ray will penetrate to a depth of 3 mm. of mucous membrane, and can be so regulated that 90 per cent of the rays can be absorbed where desired. Many teeth which otherwise would have been removed, have thus been saved.

*Presence of Various Grains of Factors Inhibiting Tumor Growth.* R. LEWISOHN, D. LASZLO, C. LEUCHTENBERGER, R. LEUCHTENBERGER, AND Z. DISCHE. *Proc. Soc. Exper. Biol. & Med.*, 52: 269, April, 1943.

Groups of 7 mice are matched with respect to tumor size 7 to 10 days after inoculation with sarcoma 180. If one of these groups is injected intravenously with saline twice daily for 2 consecutive days, the tumor sizes and tumor weights of the injected animals and controls will agree after 48 hours. If a group is similarly injected with a standard yeast extract, the tumor growth in this group is significantly inhibited.

It was found that 4 intravenous injections of 0.1 cc. of standard yeast extract (corresponding to 5.25 mg. solids) produced a significant inhibition of tumor growth if the mice were fed a normal diet. If, however, the mice were fed a polished rice diet, 4 injections of 1.75 mg. solids of the same standard preparation produced a similar inhibition. A number of experiments indicated that the increased inhibition was not due to dietary deficiency nor caloric restriction. One-tenth of a cubic centimeter of an aqueous extract of the rice, corresponding to 2.4 mg. solids, inhibited tumor growth to about the same extent as did the standard preparation.

Similar feeding experiments were done with pearled barley, malted barley, wheat flour, wheat germ, oats, corn meal, and soya beans. The pearled barley and soya beans increased the inhibitory effect; the wheat flour, oats, and corn meal did so to a lesser extent; while no effect followed the feeding of malted barley and wheat germ.

Extracts of pearled barley produced inhibition similar to that effected by the standard preparation when groups of mice were held on a normal diet; a malted barley extract was ineffective.

*The Shwartzman Phenomenon in the Genesis of Pulmonary Abscess.* J. COHEN AND S. E. MOOLTEN. *Arch. Path.*, 35: 517, April, 1943.

Previous studies have demonstrated that pure cultures of the anaerobic microorganisms recovered from the usual mixed flora of putrid abscess of the lung in man are incapable of reproducing the lesion in animal experiments. Exceptionally certain anaerobic bacilli have been found which are pathogenic in pure culture. One such bacillus is described in the present report with special reference to the mechanism of its action when it is introduced intratracheally into the lung of a rabbit. Culturally and otherwise it resembled *B. necrophorus*. From the point of view of morphology the lesion caused by it appeared to be specific. In the genesis of this lesion, studied in various stages, the primary incident was seen to be lobular atelectasis, which provided an anaerobic environment for the survival of the bacterium. Forced inhalation of a mixture of oxygen and carbon dioxide largely prevented the development of the lesion. Dense leukocytic infiltration and necrosis quickly followed the primary atelectasis and formed a sharply demarcated consolidation ending in abscess with or without empyema. The factors in the production of necrosis by this anaerobe were studied by application of the principles of the Shwartzman phenomenon. Earlier experiments had shown that pure cultures of the usual anaerobic bacilli found in putrid abscess of the lung failed to produce potent skin-preparatory toxins for the phenomenon, although active in producing potent provocative toxins. Conversely, the exceptional

anaerobic bacilli which were pathogenic in pure culture were capable likewise of producing potent skin-preparatory toxins. In the experiments reported here, the capacity to produce a necrotizing lesion in the lung of the rabbit was abolished by subculturing the anaerobe in the presence of bile. Nevertheless the capacity to produce potent skin-preparatory and lung-preparatory toxins endured, as proved by the production of necrotic lesions in prepared sites in the skin and the lungs, respectively, by injecting potent provocative toxins intravenously at a suitable interval, in accordance with the requirements for elicitation of the Shwartzman phenomenon. The lesions thereby produced in the lungs were identical with those produced in a primary manner by virulent cultures.

*Primary and Secondary Sexual Characteristics.* W. A. SHONFELD. *Am. J. Dis. Child.*, 65: 535, April, 1943.

A method of measuring the size of the penis and testes is described which was found to be both clinically and statistically reliable and valid. The measurements taken were the length and circumference of the fully stretched flaccid penis and the volume of each testis. The length of the penis was measured on the dorsal surface with an ordinary centimeter ruler and its circumference with a special set of gauges. The volume of the testes was determined by comparing them with standard models of known volume. Fifteen hundred normal boys and men varying in age from 1 day to 25 years were studied as to range of size of the penis and testes, size and shape of the prostate and extent of maturation of the secondary sexual characteristics; these variables were all correlated with chronologic age. The measurements of the penis and testes are graphically presented, showing the trend of growth. During the first two years, there is only slight growth of the testes and increase in the circumference of the penis, while the length of the penis continues to grow until about 4 or 5 years of age. After this initial slight growth there is no appreciable change throughout prepubescence until the onset of pubescence, when there is a rapid spurt reaching its maximum during the post-pubescent period. The variation as to the age at the pubescent spurt and the rapidity of its development is so great that there is a wide range of normal between 10 and 18 years of age. The actual measurements and their percentile distributions are charted. The secondary sexual characteristics have been correlated with the size of the testes and penis and graphically presented by subdividing biologic maturity into six arbitrary subdivisions. The age distribution of each of these groups was also studied.

*The Chemistry and Mechanics of Hydrochloric Acid Formation in the Stomach.* F. HOLLANDER. *Gastroenterol.*, 1: 401 April, 1943.

This is a detailed formulation of the author's hypothesis concerning the mechanism of formation of gastric HCl, and includes a comprehensive and critical review of the literature relating to each major phase of the process. Evidence is weighed on various questions, with the following conclusions: 1) HCl is formed by the parietal cells, not by the mucosa acting *in toto* as a membrane of specific permeability. 2) Free acid first occurs either in the cytoplasm immediately adjacent to the intracellular canaliculus, or in the canalicular wall. 3) As it is formed at this site, the parietal secretion is an isotonic (or slightly hypertonic) solution of HCl, which may contain HBr and HI when these are present in the blood stream, but nothing else. 4) The immediate source of the Cl is the blood and lymph, not a special depot elsewhere in the body. 5) The duration of the entire process, starting with blood Cl and ending with the ejection of acid into the gastric cavity, is less than 1 minute. 6) The immediate source of H-ion is either water or acid buffer salts of the parietal cytoplasm. The acid is formed by the hydrolysis of the neutral chlorides, the residual alkali being neutralized immediately by intracellular buffers and returned to the general circulation via the interstitial fluid. 7) In order to account for the complete separation of HCl from the reactants and other cell constituents, it is hypothesized that the wall of the intracellular canaliculus is a membrane, irreciprocally permeable to halide-ion and water only. Stimulation of the parietal cell forces water into the canaliculus, and this takes H-ion and Cl-ion along with it, thus effecting a membrane hydrolysis of the neutral chloride and, simultaneously,

a separation of the HCl. 8) Isotonicity is attained coincidentally with fluid transfer across the membrane, i.e., the process constitutes a "steady state." 9) Concerning applicability of the all-or-none law, there is as yet insufficient evidence. 10) Fatigue of the parietal cells does not occur so long as an adequate supply of water and Cl is maintained. 11) The energy requirements are analyzed into chemical, electrical, mechanical and osmotic work—the latter being zero. 12) No evidence has been adduced regarding the mechanism by which this energy is provided, but several possibilities are suggested.

*Tumors of the Brain in Children and in Adolescents. A Clinical and Anatomic Survey of Ninety-two Verified cases.* J. H. GLOBUS, J. M. ZUCKER, AND J. M. RUBINSTEIN. *Am. J. Dis. Child.*, 65: 604, April, 1943.

Ninety-two verified cases of tumor of the brain encountered in children and adolescents are surveyed clinically and anatomically.

While on the whole, expanding intracranial lesions in persons of these age groups (from infancy to 16 years of age) behave clinically in a way similar to those occurring in older persons, they exhibit some clinical departures which deserve attention.

Among these deviations is the frequent absence of papilledema associated with tumors localized in the pons, a situation which causes severe internal hydrocephalus and hence should be a more common cause of choked disks.

There is also the greater incidence of manifestations of vegetative dysfunction, expressed in retarded or accelerated development of secondary sex characters. These manifestations are of course readily explained by the greater incidence in children of suprasellar tumor (craniopharyngioma), which by direct pressure causes anatomic and hence physiologic disturbance in the tuber cinereum, the seat of the centers controlling vegetative activity. The same holds true for pinealoma, which exercises its influence on the hypothalamus indirectly by blocking the iter and thus causes hydrocephalus, which in turn causes the excessive thinning, stretching and disruption of the floor of the third ventricle, including the tuber cinereum. Indeed, older persons do not altogether escape such an effect, although, as regards sex characters, regression is the more common disturbance in them.

In line with the foregoing manifestations is the occasional symptom of abdominal distress or obstipation, both conditions probably being central in origin.

Another striking feature for which no explanation is yet available is the low incidence of tumors in children between the ages of 6 and 10 years.

As to the types of tumor prevalent in children and adolescents, it seems that the autochthonous blastomatous tumors predominate, an observation which supports the view that cerebral neoplasms in the majority of instances probably originate from embryonal rests. The best examples of such tumors are craniopharyngioma, pinealoma, ependymoma and hemangioendothelioma.

Trauma to the head, although recorded in a few cases as marking the onset of symptoms of intracranial involvement, is found to be of no significance as a precipitating or accelerating cause of growth of the tumor.

Surgical intervention accomplishes much for patients with a tumor of the hemangioma-tous group and holds out fair promise for some with craniopharyngioma, but with the latter growth the surgical results are best when they are of a more conservative character.

The value of roentgen therapy cannot be estimated with any degree of accuracy on the basis of the small numbers of cases available for this study in which this treatment was used, but there is evidence that it deserves further trial and study.

*Fat and Vitamin A Absorption in Sprue and Jejuno-Ileitis.* D. ADLERSBERG AND H. SOBOTKA. *Gastroenterol.*, 1: 357, April, 1943.

For the study of intestinal absorption two function tests were adopted: the fat tolerance test and the vitamin A tolerance test. Active sprue is characterized by a failure of absorption which manifests itself in complete lack of elevation of the lipids or of the vitamin A content of the serum, after the ingestion of a standard dose of butter fat or vitamin A, respectively. However, during a remission, a fairly satisfactory fat and vitamin A absorp-



tion is found. The nature of the impaired absorption in sprue is as yet unknown, although there are indications that tropical as well as non-tropical sprue and celiac disease are caused by deficiency of some essential dietary factor.

In contrast to sprue, cases of extensive granulomatous jejuno-ileitis show a fairly satisfactory fat and vitamin A absorption in the tests. Apparently, small areas of non-diseased intestinal wall and possibly even the diseased areas are able to absorb fat and vitamin A, whereas in sprue there is a generalized inhibition of absorption in each individual cell of the intestine.

The possibility of a functional differentiation between sprue and jejuno-ileitis is of practical importance. While in typical cases of either disease the clinical picture, the radioscopic and radiographic examination of the small intestine and the laboratory findings (blood picture, stool analysis, etc.) lead to a correct diagnosis, in milder and borderline cases the differentiation may be difficult.

*Analysis of Oral Reactions to Dilantin-Sodium.* L. STERN, L. EISENBUD, AND J. KLATELL. J. Dent. Research, 22: 157, April, 1943.

This analysis is based on a two year study of 50 selected epileptics receiving dilantin. 52 per cent of patients showed gingival reactions in four grades of severity, the characteristics of which are described. The degree of hyperplasia seemed to be correlated with the length of the therapeutic period, but not with such factors as dosage, salivary output, nutritional deficiencies, or the co-administration of phenobarbital. Withdrawal of dilantin brings about a partial resolution of the hyperplasia.

Three methods of treatment are described, of which conservative periodontal treatment is the one recommended.

*The Nature of the Urethral Caruncle.* J. NOVAK. Urol. & Cutan. Rev., 47: 4, 217, April, 1943.

The urethral caruncle is a formation which occurs only in elderly women. It develops from an ectropium of the posterior wall of the urethra and is caused by postmenopausal shrinkage of the underlying vaginal tissue. All the further changes of the everted mucosa are secondary and caused by the altered environmental conditions. The caruncle has nothing to do with former inflammation of the urethra or the bladder. The inflammation is only a secondary condition. A thorough excision of the whole everted mucosa with careful suturing of the wound and narrowing of the orifice gives better results than the usual cauterization.

*Tumors in the Region of the Cauda Equina. A Review of Twenty-five Cases.* I. COHEN AND A. KAPLAN. Am. J. Surg., 60: 36, April, 1943.

Twenty-five cases in the region of the cauda equina were reviewed, this number represented 18.5 per cent of the total number of spinal cord tumors in the authors' series. The similarity both in the history (including at times trauma and remissions) and the physical signs in the early stages of tumor to those noted in protruded intervertebral disc is pointed out. The importance of this in the face of the limited exposure now employed in the operation for the removal of a protruded disc is obvious. The cases were considered under three groups: 1) those with advanced signs (5 cases); 2) those with early signs (16 cases); 3) those with absent neurological signs. The earliest symptom is pain in the lumbar region with radiation into the lower extremities. This may be unilateral. Motor weakness and reflex loss often precede the sensory changes. An elevated total protein in the spinal fluid is the most important single laboratory aid in making a diagnosis. There was no operative mortality. The most frequent type of tumor was the neurofibroma, found in 10 cases.

*An Outbreak of Dermatitis from Airplane Engine Covers.* L. SCHWARTZ AND S. M. PECK. Public Health Reports, 58: 625, April, 1943.

An outbreak of dermatitis was observed among workers manufacturing airplane engine covers made from a special plioilm. R. M. F., a chemical added to the plioilm to prevent



deterioration from light, was found to be the actual cause of the outbreak. R. M. F. is both a primary irritant and a sensitizer.

*A Statistical Method for Evaluating the Results of Treatment for Peptic Ulcer.* F. HOLLANDER AND S. MAGE. Surg. Gynec. & Obst., 76: 533, May, 1943.

This report is introduced with a review of the procedures which have been employed by clinical investigators for evaluating the results of their therapeutic (chiefly surgical) methods for peptic ulcer. Following a discussion of the statistical weaknesses of these procedures and of certain fundamental conditions which must be adhered to in order to insure statistical validity to any such procedure, the authors present a statistical procedure of their own which conforms to these requirements. Particular emphasis is placed on errors arising from random variations. Although the paper is concerned primarily with methodology, the new technique is illustrated by means of three sets of data from the records of The Mount Sinai Hospital for cases of duodenal ulcer which had been subjected to subtotal gastrectomy during the years 1923-1934. The median trend curves which were obtained indicate the existence of a plateau beyond the 10th year—which means that, in all likelihood, any patient operated upon will develop a recurrence either during the first 10 postoperative years or not at all. From these data, the average total incidence of recurrence following subtotal gastrectomy for duodenal ulcer is in the neighborhood of 9 per cent.

*The Rôle of the Sulfonamides in Dentistry.* J. S. KLATELL. Am. J. Orth. & O. Surg., 29: 5, 255, May, 1943.

The general principles which guide the physician and surgeon in their use of the sulfonamides are equally applicable to oral and maxillary wounds and infections. These drugs are an important addition to our armamentarium, but can not replace the fundamental rules and technique of surgery.

The sulfonamides are especially effective against the beta hemolytic streptococcus, *Streptococcus viridans*, and the *Staphylococcus aureus* organisms, which are commonly identified with dental sepsis. Thus the drugs have come to play an important rôle in the therapy of acute alveolar abscess, osteomyelitis of the jaws, cellulitis of the face or neck, and general sepsis of dental origin. The drugs are also being administered prophylactically to patients with rheumatic, syphilitic, or congenital defects of the heart valves, in order to lower the incidence and virulence of the bacteremia which may follow tooth extraction or other dental manipulation.

Legally and technically, members of the dental profession have the right to prescribe and use the sulfonamides for conditions arising from dental and oral infections. However, no one should avail himself of this privilege unless he is thoroughly acquainted with the nature of the drugs, their clinical pharmacology, and, especially in this group, their toxicity. It would be best for the dentist to administer the sulfonamides in collaboration with a qualified physician.

*A Comparison of Insulin and Food as Stimuli for the Differentiation of Vagal and Non-Vagal Gastric Pouches.* E. E. JEMERIN, F. HOLLANDER, AND V. A. WEINSTEIN. Gastroenterology, 1: 500, May, 1943.

On the basis of a correspondence survey to determine the criteria in use in various laboratories for the differentiation of vagal from non-vagal pouches, 6 precise tests were formulated for this purpose. Two of these involved only the psychic phase of gastric secretion (by "teasing" and by "taste"), and 4 involved a combination of psychic and chemical phases (various characteristics of the postprandial secretory curve with meat). A seventh test, employing insulin hypoglycemia under specifically defined conditions, was formulated by the authors. The unreliability of the 6 criteria employing meat was conclusively demonstrated by a comparative investigation, conducted upon 5 dogs with total vagal (Hollander-Jemerin) pouches, 5 with partial-vagal (Pavlov), and 3 with non-vagal (Heidenhain)

pouches. In only 83 out of 228 tests was the response the same as that anticipated on the basis of anatomical classification of the pouch. Results with the insulin test in 29 experiments on these same dogs were uniformly consistent with the pouch type, thus establishing the validity of this procedure. However, so far as present evidence indicates, even this test procedure is incapable of a quantitative differentiation of pouches of different "degrees of vagality."

*Primary Friedländer Pneumonia.* L. HYDE AND B. HYDE. *Am. J. M. Sc.*, 204: 5, 660, May, 1943.

The authors studied 51 cases of Friedländer pneumonia of whom 88 per cent were more than 40 years of age. The ratio of males to females was 5:1. Almost 60 per cent of all cases occurred in the 5 month period from November to May. Occupation played no rôle. This type had an incidence of 1.6 per cent of pneumonias. Several of the cases have been found to have bronchiectasis. Friedländer pneumonia is less infectious than pneumococcal pneumonia; all the lobes are about equally involved. The onset is sudden with a cough (91 per cent), sputum (90 per cent), chest pain (82 per cent) and chill (58 per cent). The patient is usually acutely ill and dyspneic, often cyanotic. The first day temperature is over 102°F. in most cases. The sputum is described as "thick," "bloody," "gelatinous" or a small hemoptysis. Positive blood cultures were present in 45 per cent. The mortality rate for bacteriemic patient was 82 per cent and for nonbacteriemic patients, 23 per cent. The chest roentgenogram usually reveals a dense homogeneous shadow of consolidation. Among the complications were meningitis, purulent pericarditis and several apical spontaneous pneumothoraces. Pleural effusion was present in 8 patients, purulent in 3. The diagnosis is simple if Friedländer pneumonia is borne in mind. Routine sputum and blood cultures on all patients with pneumonia is indicated. The gross mortality rate was 51 per cent of all deaths, 80 per cent occurring within five days of hospitalization. It would seem that sulfadiazine may be the drug of choice in this disease. However, chemotherapy has proved to be of very questionable value in most cases and a final decision must be withheld.

*Adrenal Cortex in Systemic Disease. A Morphologic Study.* E. L. SARASON. *Arch. Int. Med.*, 71: 702, May, 1943.

The adrenal glands of 110 patients were studied in an effort to correlate cortical changes with systemic disease. Cortical enlargement associated with depletion of lipid or reversal of lipid pattern was found associated with inflammatory diseases, cachexia, pemphigus and protracted emesis. Cortical enlargement with an increased amount of lipid was encountered in cases of hypertension; the change was more striking when the hypertension was associated with primary vascular disease. The explanation of these changes is not at hand. No significant alterations were present in the series of cases of atherosclerosis. Extreme enlargement was found in four cases of erythroblastosis fetalis. This study serves to emphasize that the enlargement of the adrenal cortex and the depletion of lipid are reflections of the metabolic disturbances associated with certain systemic diseases and not the direct effect of the latter.

*Testicular Tubular Adenoma in Two Sisters.* J. NOVAK. *Am. J. Obst. & Gynec.*, 45: 856, May, 1943.

The author reports on two sisters with female exterior and female sexual desire, but with gonads which consisted preponderantly of underdeveloped testicular tissue and a benign testicular tubular adenoma. The ovarian tissue was represented only by islands of ovarian stroma. In spite of the almost exclusively male character of the gonads, the same deficiency symptoms developed as after bilateral ovariectomy. The genealogy of these sisters revealed, that there were many members in the kindred with sexual abnormalities. Goldschmidt's intersexuality theory was applied to explain the origin of this rare gonadal malformation.

*Antipressor Effects of Orthoquinoid Epinephrine Derivatives in Experimental Hypertension in the Rat.* K. A. OSTER AND H. SOBOTKA. *J. Pharmacol. & Exper. Ther.*, 78: 100, May, 1943.

Adenochrome derivatives, when administered parenterally, lower the blood pressure of experimentally hypertensive rats, but do not affect the blood pressure of normal animals. No toxic manifestations or fever are observed. The halogeno-adrenochromes fulfill for the rat the requirements postulated for an antipressor drug. Acute experiments eliminate, as explanation of the observed effects, a parasympathomimetic, direct muscular, or sympatholytic mechanism. The catabolism of pressor amines is discussed and a chemical mechanism for the antipressor effect of quinones is suggested with due regard to species differences.

*Ambulatory Insulin Shock Technique in the Treatment of Schizophrenia.* P. POLATIN AND H. SPOTNITZ. *J. Nerv. & Ment. Dis.*, 97: 5, 567, May, 1943.

The report represents an attempt at a complete evaluation of the results of studies of the effects of ambulatory insulin shock technique in the treatment of patients with schizophrenia.

Thirty-six out of forty-four patients treated showed a definite clinical improvement. The improvement occurred in four progressive stages. The duration of the treatment necessary for improvement was dependent upon: (a) the length of time of the psychosis before treatment, and (b) the pre-psychotic personality of the patient. As a general rule, the patient had to be treated as long as the psychosis had existed prior to treatment, in order to obtain a recovery response.

*Shrapnel in Sphenoid Sinus Causing Blindness, Removal with Recovery.* I. B. GOLDMAN. *Laryngoscope*, June, 1943.

The author cites a case of prompt restoration of vision following extraction of shrapnel from the sphenoid sinus, which had previously suggested an hysterical amblyopia. The idea of hysteria was augmented by the tubular vision in the left eye. Prompt return of vision after the operation is sometimes seen in other conditions such as retrobulbar neuritis or an optic neuritis following sinus operations when affected foci in the sinus are responsible for their presence. The position of the optic nerve in its relationship to the sphenoid sinus is important in evaluation of both contralateral and unilateral symptoms. Removal of pressure of the shrapnel in the lateral wall should explain the rapid return of vision.

*Pheochromocytoma of the Adrenal Gland.* A. HYMAN AND W. H. MENCHER. *J. Urol.*, 49: 6, June, 1943.

Pheochromocytoma of the adrenal gland is a tumor of the medullary portion, producing hormonal symptoms. This type of tumor affords the opportunity to study the effects in humans of prolonged excessive discharge of adrenalin into the general circulation. This type of tumor causes a surgically remediable form of paroxysmal hypertension. The diagnosis of pheochromocytoma is based on (a) the typical symptomatology during an attack, (spontaneous or induced), (b) the typical pressor response mechanisms, (c) the demonstration of pressor substance in the blood of a patient during the height of an attack, (d) the demonstration of the tumor by perirenal insufflation. Four cases of pheochromocytoma of the adrenal gland are presented. Three cases occurred in women and the fourth occurred in a male. All the tumors were removed successfully and all the patients made an uneventful recovery. A long period of follow-up in all these cases reveals that the patients are in excellent health and that no further attacks have occurred. The problem of preoperative, operative and postoperative care is discussed.

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## THE EDWARD GAMALIEL JANEWAY LECTURES

## ASPECTS OF THE TRANSMISSION OF THE NERVOUS IMPULSE

## I. MEDIATION IN THE PERIPHERAL AND CENTRAL NERVOUS SYSTEM

OTTO LOEWI, M.D., Sc.D. (Hon.)<sup>1</sup>

The Edward Gamaliel Janeway lectures are expected to center around the work of the lecturer. Since for more than twenty years I have worked on the chemical transmission of nervous impulse, I decided to lecture about this field in which I have acquired a reputation of an expert. I accept this honoring title if you accept my definition of an expert: an expert is a man who knows much more than anybody else about the gaps in his field.

I have chosen the topic in spite of the fact that six years ago Sir Henry Dale (1) covered a part of this subject in his Welch lectures. This in my opinion is no objection to another lecture in the same field. The essence of a lecture does not, or at least should not, merely consist in an enumeration of facts with which in most cases the audience may be familiar anyway but it should in addition offer the opportunity of getting a picture of the personality of the lecturer. This is at least partly afforded by the fashion in which he puts things together and by the manner in which he looks upon them. This is obviously different with different scientists as it is with different artists dealing with the same object and would by itself justify a fresh presentation of the topic. In addition as I have had the good fortune to open up the whole field it may be of some interest at least for those who have not been particularly concerned with the subject to learn from the author himself how the whole question arose and was developed. Last but not least within the last six years there have accumulated new facts, views and problems to such an extent that in the span of two lectures I cannot deal with all of them, even by restricting to the utmost the discussion of the material which was covered in Sir Henry's lecture.

As you all know, a main function of the central nervous system consists in the control of the bodily functions according to its needs. For the most part the central nervous system is informed of these needs by messages reaching it through the afferent nerves. It answers these messages by sending out impulses which eventually reach the effector organs by way of the efferent nerves and thereby induce the appropriate functional changes. The mechanism by which the nervous impulse is transmitted to the effector organ was not understood. One only knew the following: if a nerve is stimulated in natural fashion from its central origin or artificially during its course there is produced as in every stimulated living tissue an excitation. This means a change of energy whose intimate

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nature so far is unknown. Within the nerve this excitation is propagated. This propagated impulse is, as you know, accompanied by an electrical wave, the action current. It was generally believed that this electrical wave spreads to the effector organ and there elicits the specific reaction. Such an assumption, however, had to meet with difficulties; among them a great one has been raised from the following consideration: one can easily understand that an electrical wave, raised by the stimulation of a nerve and spreading to its effector organ, there initiates or increases its activity. But how can one understand that the same electrical wave in the case of the so-called inhibitory nerves does not initiate or increase the activity of the effector organ but does actually decrease or even stop it? Since in this way the assumption of an electrical mechanism of the transmission of a nervous impulse to its effector organ proved to be unsatisfactory, another mode of transmission had to be taken into consideration and had in fact been considered, namely a chemical one. At the International Physiological Congress in Boston in 1929 a former co-worker of mine the late Sir Walter Morley Fletcher reminded me that as far back as in 1903 I had expressed the view that since certain drugs mimic the stimulation of autonomic nerves, it may be that these nerves in their turn may act by liberating from their terminals chemical substances and in this way transmit the nervous impulse to their effector organs. Since that time several scientists especially Elliott in 1904 (2) and Dixon in 1907 (3) have made the same assumption. But it was not until 1921 that I was able to prove the correctness of this view by a very simple experiment. Though most of you may be familiar with it, I cannot avoid describing it briefly with regard to the fact that this very experiment represents the fundament of the whole theory of the chemical transmission of nervous impulse.

I isolated the hearts of two frogs, one with its nerves, one without. The first heart may be designated as the donor heart, the second as the recipient heart. In each heart I inserted a glass cannula filled with a small amount of Ringer solution. For a short period the vagus nerve connected with the donor heart was stimulated with the usual effect: decrease of frequency and amplitude of the heart beat. Now I transferred the fluid of this heart to the recipient heart with the result that it behaved exactly like the donor heart during vagus stimulation and exactly like the effect of this the effect of the content of the heart obtained during vagus stimulation was annulled by atropine. When instead of the vagus I stimulated the accelerator nerve of the donor heart and transferred its content to the recipient heart this again produced exactly the same effect as the nerve stimulation of the donor heart: increase of frequency and amplitude. By these experiments was proven that the nerves do not influence the heart directly but that the immediate effect of their stimulation consists in liberation of chemical substances from their endings and that these very substances cause the characteristic modification of the heart action as described above. In other words the nervous impulse is transmitted to the heart not directly but indirectly by chemical substances which we may call transmitters.

It seemed probable from the beginning that the mechanism of chemical transmission would not be limited to the special case of the heart but would be true

for other organs too. We shall soon see that this presumption was right. But first, in view of what is to follow, we have to deal with the character of the substances released by nerve stimulation.

I should like to start with the transmitter of vagus impulses which at that time I called "Vagusstoff" and tell how I succeeded in identifying it. At the time of the discovery one was familiar only with one substance to be found in the organism whose effects—at least in certain respects—mimic the effect of vagus stimulation. It was choline. The vagusstoff, however, could not be choline since the effect of choline if introduced in the heart lasts for a long time, whereas the effect of the vagusstoff fades quickly. What other substance could be considered? In 1906 the distinguished Harvard Pharmacologist Reid Hunt had found (5) that some cholinesteres are very much more effective than choline itself and that their effect is transitory. Starting from this discovery, already by 1922 I had assumed that the vagusstoff might be a cholinester. This assumption later on, as you now know, proved to be true. It could be shown that the course and mode of action of vagusstoff and of a certain cholinester, Acetylcholine (Ac.Ch.), are indistinguishable. This is true also for the quickly fading effect of the two substances mentioned above. What is the cause of this fading? It seemed most probable that it is caused by a hydrolyzing enzyme. I was able to prove the correctness of this view again by a very simple experiment (6). I prepared a watery extract of the heart and divided it in two halves. Since most of the enzymes are destroyed by heat I heated one half. Then I added to both halves vagusstoff or Ac.Ch. and incubated them for a while. Then I tested them on the frog's heart with the result that in the heated sample the added substances were undiminished whereas in the non-heated one they were completely destroyed. The splitting enzyme later on was called cholinesterase.

Another hint as to the identity of vagusstoff and Ac.Ch. was the following: It had been known for a long time that the transitory action of vagus stimulation is markedly prolonged by previous application of very small doses of eserine. I just mentioned that the quick fading of the effect of vagusstoff and of Ac.Ch. is caused by the action of cholinesterase. This suggested to me the possibility that the prolongation of the vagus action as produced by eserine was due to an inhibitory action of this alkaloid on cholinesterase. I could definitely prove that this was the case (7). Hence it occurs that after previous application of eserine the action of vagusstoff and of Ac.Ch. is enhanced and prolonged exactly like the action of vagus stimulation. It was this discovery of the esterase inhibiting action of eserine which made possible the later extension of the proof of the occurrence of neurochemical transmission by Ac.Ch. to a very wide range of effects. On the one hand the inhibition of esterase activity by eserine protecting Ac.Ch. from being split has made it possible to preserve and therefore to detect minute traces of vagusstoff released by nerve stimulation. On the other hand in cases where it is impossible to prove directly the presence of Ac.Ch. by nerve stimulation we are in general entitled to assume that the stimulation acts by releasing Ac.Ch., whenever the effect of the stimulation is enhanced by previous eserineisation.

Finally, since Dale and Dudley (8) later on succeeded in isolating Ac.Ch. from animal organs, there is no doubt that the vagusstoff is Ac.Ch.

In regard to the nature of the sympathetic transmitter, I was able to show as early as 1921 that the transmitter shares many qualities with adrenaline. Both for instance are destroyed by alkali, by fluorescent and ultra violet radiation, the effect of both is abolished by ergotoxine and as was shown (9) later on in Cannon's laboratory enhanced by small doses of cocaine, the sensitizing effect of which on adrenaline action was found by Froehlich and myself about 30 years ago (10). Like the effect of adrenaline the effect of the sympathetical transmitter applied to the heart also fades very slowly. After all it seemed very likely that the sympathetic transmitter was adrenaline. But it was not until 1936 that I was able to show that the sympathetic transmitter is actually adrenaline (11).

How did I succeed in proving this? British chemists (13) had observed that adrenaline even in a dilution of  $10^{-8}$  shows in the light of a mercury lamp a beautiful apple-green fluorescence on addition of a little alkaline. According to Gaddum and Schild (12) substances related to adrenaline show this reaction only in concentrations of a much higher order of magnitude. This fluorescence, specific for adrenaline, in body fluids and organ extracts, however, is overshadowed by the presence of colloids. I therefore applied the reaction on heart extracts which I dialyzed in order to get rid of the disturbing colloids (11). The dialyzates showed a marvelous green fluorescence. But how to find out whether the substance released by nervous stimulation was adrenaline? According to results of titration experiments with adrenaline on the frog's heart the content of the fluid present in the heart during a stimulation of the sympathetic amounted only to about one tenth of the minimal dilution showing just a faint fluorescence. I therefore was obliged to reach a higher concentration. Unfortunately it has been impossible to concentrate an adrenaline containing watery solution without destroying the adrenaline. Hence I got the idea to enrich the fluid filling the heart during sympathetic stimulation with the transmitter. I succeeded by using for the filling of the heart during often repeated stimulation always the same one cc. of fluid. This fluid finally on addition of alkaline showed a definite green fluorescence. Hereby was proved that the substance released by sympathetic stimulation is adrenaline. In this country it is often called sympathin. In fact sympathin is identical with adrenaline. The use of the word sympathin originates from the following: W. B. Cannon and A. Rosenblueth (14) reported that on stimulation of postganglionic sympathetic fibres remote organs provided with sympathetic nerves react under the condition that they were sensitized to adrenaline by previous degeneration of their sympathetic nerves. They claimed that the kind of reaction of the remote organs correspond to the kind of answer of the stimulated organs. In other words it was of inhibitory or augmentory or mixed character. They therefore assumed that the substance released by nervous stimulation combined with the substance in the stimulated organ and that this combination which they called inhibitory or excitatory sympathin was conveyed by the blood to the remote organs. Cannon (15) agrees, however,

that the substance released by sympathetic nervous stimulation, and we are only dealing with this, is adrenaline.

And now we can proceed to discuss the extent to which the principle of the neurochemical mechanism discovered at the frog's heart is valid. First it could be shown that this mechanism holds true for the transmission of the nervous impulse on the heart of mammals too. The nerves of the heart, the vagus and the accelerator, belong as you know to two different nervous systems, which together represent the autonomic nervous system. The vagus belongs to its parasympathetic, the accelerator to its sympathetic division. Hence it was from the beginning to be expected that the neurochemical mechanism of transmission would apply to the other nerves of the autonomic system too. The correctness of this view was tested in a very wide range of cases. It is needless to go into many details concerned with this point since Dale in his Welch lecture has extensively reviewed the whole material. It may suffice to summarize the results of the experiments by saying that in all cases studied the effect of nerve stimulation is due to the release of a chemical transmitter.

As to the nature of the transmitters released by stimulation of postganglionic parasympathetic and sympathetic nerves it may be said that most parasympathetic nerves release Ac.Ch., most sympathetic ones adrenaline. But there exist some exceptions in that the stimulation of some nerves belonging anatomically to the parasympathetic system leads to the liberation of adrenaline and on the other hand stimulation of some sympathetic nerves leads to the liberation of Ac.Ch. Dale (16) therefore distinguishes "cholinergic" and "adrenergic" fibres irrespective of their anatomical origin.

So far we only have dealt with the question as to the mechanism of transmission from postganglionic<sup>a</sup> autonomic nerves to their respective effector organs. We now shall learn that the principle of neurochemical transmission is valid to a far greater extent.

In 1914 Dale (17) had made the discovery that Ac.Ch. acts not only like muscarine on the effector organs of postganglionic nerves but also—exactly like nicotine—on those of preganglionic ones stimulating in small doses, paralyzing in large doses. This suggested the examination as to whether on nervous stimulation Ac.Ch. is not released from there too and acts as transmitter. The first observation in this line was made by Feldberg (18). He was able to show that preganglionic stimulation of the splanchnic liberates Ac.Ch. and by this way stimulates the adrenal medulla to secrete adrenaline exactly like Ac.Ch. if injected. Since the cells of the adrenal medulla are modified ganglionic cells, Feldberg's finding suggested the investigation whether Ac.Ch. is not also the transmitter from preganglionic fibres to ganglia. This at first sight did not seem to be very likely for the following reason. In the cases which we have dealt with hitherto the effect of nervous stimulation on their effector organs is a relatively slow one, in the case, however of stimulation of preganglionic fibres running to the ganglia the effect starts almost immediately and by stopping the stimulation almost immediately ceases. In this case therefore because of the speed of action it was hardly to be expected that the transmission was due to a chemical



event consisting in the liberation, diffusion, action and removal of a chemical substance. And yet in Dale's laboratory (19) during preganglionic stimulation of the superior cervical ganglion perfused with eserinizied Locke solution Ac.Ch. was detected in the effluent in an amount sufficient to stimulate the ganglion. When the stimulation was continued to the point of exhaustion the reaction of the ganglion ceased and at the same time Ac.Ch. disappeared from the perfusion fluid. After an interval during which stimulation had been stopped the reaction returned and Ac.Ch. reappeared. After strong nicotization or curarization, stimulation still liberated Ac.Ch. but the ganglion did not react to it nor to Ac.Ch. if injected. This means that nicotine and curare do not paralyze the nerve-endings but prevent the sensitivity of the ganglion to Ac.Ch.

The results of these experiments suggested to Dale and his co-workers to investigate the nature of transmission in another case where also the effect of nerve stimulation almost immediately appears and vanishes: namely in that of the spinal nerves running to the striated muscle. They found (20) that close arterial injection of small doses of Ac.Ch. raised a quick contraction which resembled slow single twitches. As within the ganglia large doses of Ac.Ch. prevented the effect of stimulation exactly like curare. Furthermore, Ac.Ch. was found in the eserinizied perfusion fluid after indirect stimulation. Direct stimulation of the muscle after nervous degeneration though it contracted strongly did not release a trace of Ac.Ch. This proves that Ac.Ch. found in the perfusion fluid of the muscle which was stimulated indirectly was not a product of muscular activity but was liberated from the nerve-endings. Finally curare was shown to inhibit the effect of Ac.Ch. exactly like that of nervous stimulation and previous eserinziation caused the response to a maximal nerve volley to change from a single twitch to a repetitive response of the nature of an evanescent tetanus.

Before we draw the obvious conclusions from the experiments just quoted I should like to draw your attention to important analogies disclosed by some of the facts which we have discussed just now. They are, so to say, by-products and present a progress of our physiological knowledge reached so often by purely pharmacological means. As we have seen Ac.Ch. influences in the same manner the cells of the adrenal medulla, the ganglia, and the motor end-plate stimulating them in small, paralyzing them in large doses. Nicotine has exactly the same effect. Curare, while having the same points of attack, has a paralyzing effect only. All this means that there exists a close analogy between the cells of the adrenal medulla, the ganglia, and the motor end plates in as much as their pharmacological reaction is concerned. This analogy is easily understood. The cells of the adrenal medulla are modified ganglion cells and the cells of the motor endplates are also neurogenic since they are derived from the cells of Schwann's sheath. Considering the close analogy between the pharmacological reaction of the motor end-plates and the autonomic ganglia, we may be allowed as Elliott (21) has already suggested 40 years ago to look upon the muscle fibres as upon a kind of equivalent of postganglionic fibres. Consequently, the much discussed question as to the mode of propagation of the impulse from the motor end-plate to the muscle fibres would coincide with the question as to the mode of propaga-

tion of impulses from the ganglion to the postganglionic fibres. At all events, by the disclosure of the analogy existing between the motor end-plate and the autonomic ganglion, the basic difference assumed till now to be existing between the structure of the peripheral autonomic and spinal neurons respectively, ceases to exist.

If we now summarize and consider the results of the investigations concerning the transmission of nervous impulse at the synapses of slowly reacting organs like the postganglionic effector organs and the adrenal medulla on the one hand the rapidly reacting organs like the ganglia and the striated muscles on the other hand, we find an almost complete analogy: in all these structures a perfusate obtained during the resting state contains practically no Ac.Ch. In all of them nervous stimulation causes its appearance in the effluent. In all of them perfusion with Ac.Ch. induces the typical effect of nerve impulses. In all of them certain drugs—atropine in postganglionic effector organs like the heart, nicotine and curare in the ganglia and striated muscles—block the effect of Ac.Ch. At the same time they block the effect of nervous stimulation.

Taking into consideration all these analogies everything seems to fit in perfectly with the assumption that the chemical mechanism of transmission is valid everywhere at peripheral synapses, whether—to use an expression of Eccles (22)—the transmission is of long or of short duration. And yet quite a few neurophysiologists especially in this country accept the chemical theory only as far as it concerns the slow transmission of nervous impulses from postganglionic fibres to the respective effector organs. In regard to the transmission of short duration in ganglia and muscles, they admit that by nervous stimulation Ac.Ch. is liberated from preganglionic autonomic and spinal nerve terminals exactly as it is liberated from postganglionic nerve endings and that Ac.Ch. when perfused acts there exactly like the nervous impulse. In spite of this they oppose the theory that in the cases of short duration the mechanism is chemical.

It is impossible to go into all the details of their argumentations. It may suffice to discuss their most pertinent objections. The first concerns the fact that eserine though it preserves Ac.Ch. from being destroyed did not produce in some experiments a repetitive discharge from the superior cervical ganglion. Dealing with this objection Dale (1) already emphasized the fact that eserine by itself in more than a very low concentration has a paralyzing action on ganglia and that the persistence of Ac.Ch. in contact with these in more than a very low concentration has also a secondary depressing effect. Furthermore Rosenblueth and Simeone (23) later on were able to show that under appropriate conditions at the superior cervical ganglion eserine does slow the rate of decline of the response to Ac.Ch. Finally Bacq and Brown (25) who investigated the influence of a series of eserine substitutes on the effect on the muscle of single nerve volleys were able to show that their potentiating faculty ran closely parallel to their anti-esterasic action. By all these findings one objection against the validity of the chemical mechanism of short transmission which for years played a big part in the controversy between the proponents of the chemical and electrical theory has been removed. And now we have to consider the second pertinent objection.

This was raised by the brevity of the latent period following stimulation before action occurs in the preganglionic or spinal elements, the ganglia and the striated muscles respectively. It is true that the synaptic events at the ganglia and at the motor endplates are very brief. According to Eccles (22) in the neurons of the superior cervical ganglion the latent period of the most rapid responses ranges from 2 to 4 milliseconds and in the fibres of some skeleton muscles it may be even shorter, 1 to 2 milliseconds. In addition we have to bear in mind that the fading of the action too occurs almost immediately. The time factor as a matter of fact seemed at first sight to be an insurmountable obstacle for the acceptance of the assumption that during this extremely short period the liberation, diffusion, action and removal of Ac.Ch. could take place. Well planned experiments of Nachmansohn (26) however have revealed that at neuromuscular and ganglionic synapses cholinesterase is present in sufficiently high concentration to split within milliseconds amounts of Ac.Ch. which if released would be sufficient for a stimulating action. Though experimental data are not yet available which would establish the rate of Ac.Ch. appearance during nerve action I agree with Nachmansohn's view that there is no reason for assuming that this takes a longer time. At any rate in my opinion by Nachmansohn's findings the main objection against the acceptance of the chemical mechanism also of transmission of short duration has been removed.

Whereas the proponents of the chemical theory are able to explain any event connected with the synaptic transmission, the proponents of the electrical theory are not in the same favorable position; they have not, as have the proponents of the chemical theory, got a uniform concept which at any rate from the point of view of mental economy would be preferable but as mentioned above they accept the chemical mechanism only in the cases of transmission of long duration, whereas in the case of transmission of short duration they claim that it is the action current which spreads from the nerve endings to the effector organ and stimulates it. There already arises their first difficulty. There is no doubt that at the synapse between the nerves and the effector organs there is a protoplasmic discontinuity. So far there exists no evidence at all that the action current is able to pass through this discontinuity. In favor of their theory that it is the action current which transmits the impulse from the nerve endings to the effector organ and that it is able to act in this way proponents of this theory refer to important experiments of A. Hodgkin (27). This scientist showed that within a nerve an impulse produces an electronic potential beyond a block. In regard to this Bronk and Brink (28) made the following statement: "It is argued by some that the action current hypothesis is supported by Hodgkin's observations which favor the electrical transmission of impulses along an axon. It must be remembered, however, that the probable discontinuity at a synapse introduces physiological conditions not found in Hodgkin's experiment." Furthermore, Blair and Erlanger (29) have shown that an action current will pass an inert polarized region of the nerve and stimulate the responsive segment beyond. They contend that if the action potential can thus restimulate the axon across an inactive stretch of one to two millimeter, it is justifiable to conclude that it can excite

the tissue beyond a synapse and that it will unless the synapse includes a device for preventing current spread. In answer to this contention Alexander Forbes (24) emphasized that "the structural and presumably electrical conditions are quite different in an unbroken but inactive axon from those at the synapse. Here, at the termination of the neuron histology seems to reveal a transverse membrane which may well act as a short circuit to the action potential which is responsible to the effect observed by Blair and Erlanger. If the membrane theory of nerve conduction holds good, there is every reason to expect such a short circuiting effect at the termination of the axon. Indeed this anatomical consideration is perhaps one of the strongest reasons for seeking a different mechanism such as chemical mediation as an essential step in the excitation of the next neurone."

I had to make these quotations in order to show that the fundamental basis of the electrical theory, namely the evidence that the action current passes through the synapse, is entirely missing and that among the outstanding neuro-physiologists there are some who are even doubtful in regard to the possibility of such an event.

Furthermore, in contrast to the proponents of the chemical theory the proponents of the electrical theory have almost insuperable difficulties in explaining a great many facts. Above all: how is it to be explained that nervous excitation in one organ stimulates, in another inhibits the function? How, furthermore, to interpret the meaning of Ac.Ch. as released from preganglionic and spinal nerves if it does not own the primary function consisting in transmission of impulses. In regard to this Dale once remarked that it was unreasonable to suppose that nature would provide for the liberation in the ganglion of Ac.Ch., the most powerful stimulant of ganglionic cells, for the sole purpose of fooling physiologists. In order to meet this embarrassing fact proponents of the electrical theory offered all kinds of suggestions of secondary functions of the Ac Ch. released. For instance it may serve to increase the excitability at synapses or to delay the onset of fatigue or to dilate blood vessels locally etc. These suggestions are of purely hypothetical character. Furthermore, how to explain the following?

Nachmansohn (30) has shown that after degeneration of the respective nerves the cholinesterase content of muscle and ganglion in time declines. This loss apparently corresponds to the esterase content of the destroyed nerve endings; yet there remains even after a long time a relatively high esterase content, about 40 per cent, in the ganglia and muscles. Its location there is easily to be understood from the point of view of the chemical theory according to which Ac.Ch. released by nervous stimulation reaches the effector organs stimulates them and must be immediately destroyed there. But how to explain the great amount of cholinesterase in ganglia and muscles from the point of view of the electrical theory?

I arbitrarily picked out some few facts which are easily interpreted by the chemical theory which however offer almost insurmountable difficulties to the electrical theory. Such facts could be multiplied almost indefinitely.



Summarizing the results so far presented, I feel entitled to say that the chemical mechanism of the transmission of nervous impulses applies to the synapses of the autonomic preganglionic and postganglionic and to the spinal nerves, in other words to all peripheral synapses.

Beyond this there is missing only the proof that the chemical transmission from one neuron to the next holds true also in the central nervous system (C.N.S.). If this could be shown, it would be established that synaptic transmission is chemical everywhere in the organism. This requires a discussion as to whether there exists evidence for such an assumption. The question as to the mode of synaptical transmission within the C.N.S. concerns one of the most important and most fascinating problems in physiology. Therefore, I feel that I have to put before you its present state. It may be that you will not like it since it may not be easy to follow my guidance through this field which really represents a labyrinth. As a matter of fact there exist still as many open questions as answers. I am, however, of the opinion that a lecture should deal not only with established facts but also with gaps in our knowledge in order to stimulate work to be done in the future. As early as in 1906 Sherrington (31) suggested that the mechanism of transmission was similar at all synapses and in 1925 after the discovery of the chemical transmission at peripheral synapses he discussed the possibility of this mechanism also within the C.N.S. (32).

If Ac.Ch. is the transmitter at central synapses it might be expected that Ac.Ch. as well as cholinesterase would be located there mainly at synaptic regions. As a matter of fact Nachmansohn (33) showed that a much greater concentration of esterase was found in the gray matter than in the white and Macintosh (34) later proved the same to be true for the distribution of Ac.Ch. Suggestive are also Nachmansohn's (35) findings in regard to the relation existing between the concentration of esterase and functional development: in the brains of newborn rabbits and rats which are markedly undeveloped the enzyme concentration is very low and rapidly increases during the first three weeks after birth, almost simultaneously with the development of function in the brain. In the brain, however, of newborn guinea pigs which are already developed at that time the enzyme concentration is already almost as high as in adults.

We are, of course, not permitted to draw definite conclusions as to the part played by Ac.Ch. as transmitter of nervous impulses within the C.N.S. merely from the location of cholinesterase and Ac.Ch. respectively. We need complementary physiological evidence. This must come from two main directions: it must be shown whether or not Ac.Ch. acts like nervous stimulation upon the effector organs within the C.N.S. and secondly it must be shown whether or not during stimulation of the C.N.S. Ac.Ch. is liberated at its synapses as it is at those of the peripheral nervous system. There have been numerous investigations in both lines. It is impossible to give here a full account of them. It is in addition needless since a complete account will be published by W. Feldberg in the "Physiological Reviews," 1945. Yet, I cannot avoid going into at least some detail since the decision of the problem at hand depends not only on the results of the various investigations but also on their interpretations. I feel,



therefore, that in presenting the main material I have to give you the opportunity to get your own viewpoint. In regard to the question as to whether Ac.Ch. acts upon the C.N.S. as does nervous stimulation which is what should be expected if it is the transmitter the results obtained by a great many investigators have been quite uniform. All of them have shown that Ac.Ch. applied directly or by intra-arterial injection is able even in physiological doses to augment or to inhibit activities going on in the C.N.S. and to initiate activities there exactly as does nervous stimulation. This result taken together with the distribution of cholinesterase and of Ac.Ch. within the C.N.S. as quoted above is consistent with the assumption that it may act here as transmitter as it does in the periphery.

We need of course experimental evidence that Ac.Ch. is actually the transmitter. In order to prove this it has to be demonstrated that Ac.Ch. is released at the synapses during central stimulation. Several investigators attempted to prove this in a direct way. It would lead too far afield if I would quote and criticize the single experiments. It might be sufficient to state that they did not provide direct unequivocal evidence that stimulation releases Ac.Ch. at central synapses.

Many more experiments have been performed which approached the solution of the question at stake in an indirect way by investigating whether the antiesterases, eserine and prostigmine, by protecting Ac.Ch. incidentally released would influence the effect of central stimulation. This procedure proved to be incontestable in the studies concerned with the question of the transmission at peripheral synapses since here the antiesterases have no action by themselves but act only by protecting Ac.Ch. from being split. It has, however, not been proven thus far whether the same holds true for their action within the C.N.S. It would not be a matter of surprise if this were not the case. Probably due to the differentiation of the structure of the C.N.S. a great many drugs act quite differently here and in the periphery. I need only remind you that strychnine which has such a powerful action within the C.N.S. is almost devoid of peripheral actions, that the narcotics as well as the so-called stimulants affect the C.N.S. in concentrations far below those acting in the peripheral organs etc. We have at least to consider the eventuality that the antiesterases may act in the C.N.S. not only by protecting Ac.Ch. from being split. This consideration is needed because of the outcome of experiments in which the action of antiesterases alone, this means without accompanying stimulation, has been investigated. In these experiments the antiesterases have been directly applied on the C.N.S. or added to the perfusion fluid. The effect always consisted in an almost immediate excitation or inhibition of central functions hardly to be distinguished from that provoked by other kinds of stimulation. How to interpret these results? It has been shown that the cerebrospinal fluid and the venous blood of the brain normally do not contain detectable amounts of Ac.Ch. After the injection, however, of eserine they do contain it and an excitation of the brain starts. In analogy with the experiences made within the peripheral nervous system the most obvious explanation of these facts would be that Ac.Ch. during the normal

activity of the C.N.S. is continuously released in such an excess, that some diffuses in the cerebrospinal fluid and into the venous blood where it is immediately destroyed by cholinesterase. In the presence of eserine, however, it is protected from being destroyed and therefore accumulated to such an extent that excitation is produced. At peripheral ganglionic synapses eserine does not produce an excitation without concomitant nervous stimulation. It may be that this means only a quantitative difference between the peripheral and central action. It may, however, also mean that eserine within the C.N.S. besides its antiesterasic power exerts actions by itself which it does not exert in the periphery; for instance that it releases Ac.Ch. or that it stimulates by itself. Be that as it may; whichever interpretation we prefer, the experiments performed with eserine alone show only that eserine acts on the spot where it is applied as a local stimulus, whereby a propagated impulse is produced as by each locally produced excitation. The experiments, however, do not answer the question at stake whether or not Ac.Ch. plays a part as synaptic transmitter in the propagation of the excitation. The decision of this question could as we have seen not be attained in a direct way, namely by the investigation whether stimulation of the C.N.S. releases Ac.Ch. from the synapses. One, therefore, has as I told you before approached the solution of this question by using eserine following the same procedure which proved to be so successful in the investigations concerning the character of transmission at peripheral synapses. Here as mentioned above in cases where it is impossible to prove directly the appearance of Ac.Ch. as a consequence of nervous stimulation, one is entitled to assume that the stimulation acts by releasing Ac.Ch. whenever the effect of the stimulation is enhanced by previous eserization. Accordingly, a great many experiments were performed in the same way within the C.N.S. One has checked the effect of afferent nervous stimulation before and after previous eserization. One has performed them on different species of animals, with different procedures and antiesterases, with different doses applied in different ways and finally different reflexes were investigated. This may explain the variance in the results obtained. It is impossible to discuss here the single experiments, rather I have to limit myself to informing you on the main result. This consists in the fact that in all these experiments the antiesterases influenced the effect of reflectory stimulations or enhancing or diminishing it. In case we take the view that eserine and prostigmine also within the C.N.S. act exclusively by their antiesterasic power the results obtained tend to show that Ac.Ch. is involved as synaptic transmitter in the outcome of reflexes. And yet there exist some experiences which apparently are not consistent with this assumption. This is the reason why I am so cautious in regard to the interpretation of most of the results quoted. Of what kind are these experiences? From the outcome of experiments of Langley and Anderson (36) concerning the functional union of nerves Dale (38) has drawn the conclusion that such a union takes place only between nerves of the same character: cholinergic nerves only with cholinergic ones, adrenergic nerves only with adrenergic ones. Sensory nerves according to the experiments of Langley and Anderson (36) and to quite recent ones of Paul Weiss (41) do not functionally

unite with cholinergic nerves. Hence it seems not likely that sensory nerves are of cholinergic nature. How to find this out? Others as well as myself detected in the stems of cholinergic nerves considerable amounts of Ac.Ch. (40). Lissak (37) found in adrenergic nerves adrenaline. This parallelism was to be expected since the nerve endings releasing the respective transmitters are just a part of the nerves. With regard to the aforementioned fact that sensory nerves do not functionally unite with cholinergic ones I investigated whether or not sensory nerves contain Ac.Ch. I found none or just traces (40).

This result was confirmed by Macintosh (34) and by Feldberg (39). The latter author moreover was unable to get a synthesis of Ac.Ch. in sensory nerves under conditions where he got one in cholinergic nerves. These findings which tend to show that the sensory nerves do not behave like cholinergic nerves are obviously at variance with the aforementioned fact that the anti-esterases influence the effect of reflectory stimulation whose propagation has to pass through sensory synapses. In order to reconcile these contradictory facts one could perhaps take into consideration the eventuality that the sensory nerves might be cholinergic, that for unknown reasons, however, their stems in contrast to those of other cholinergic nerves contain no or hardly any Ac.Ch. and yet their endings do. Such an assumption however is not supported by results obtained by Macintosh (34). He found in the gray matter of the dorsal columns where a great many sensory endings make contact with the internuncial cells so little Ac.Ch. that it could hardly be determined. After all I cannot take it for granted that the sensory nerves are of cholinergic nature, in other words that their impulses are transmitted from their endings by release of Ac.Ch.

In finishing up the section dealing with the question as to whether or not Ac.Ch. is the synaptic transmitter within the C.N.S., I summarize in saying that the question is not yet solved. There exists circumstantial evidence that Ac.Ch. may be the transmitter from motor tracts, whereas it seems to me doubtful so far whether it may be the transmitter from sensory tracts.

From this whole discussion you may well realize that there is still a long, hard road to be traversed before we attain the definite solution of the problem of the character of central transmission. What does it matter? What scientist could be happy and satisfied with his life work if he would not agree with Robert Louis Stevenson: "To travel hopefully is a better thing than to arrive and the true success is to labor."

#### BIBLIOGRAPHY

1. DALE, H. H.: *J. Mt. Sinai Hosp.*, 4: 5, 401, 1938.
2. ELLIOTT, T. R.: *J. Physiol.*, 31: 20, 1904.
3. DIXON, W.: *Medical Magazine*, 1907.
4. LOEWI, O.: *Pflüger's Arch. f. d. ges. Physiol.*, 189: 239, 1921.
5. HUNT, R. AND TAVEAU, R.: *Brit. M. J.*, 1788, 1906.
6. LOEWI, O. AND NAVRATIL, E.: *Pflüger's Arch. f. d. ges. Physiol.*, 214: 678, 1926.
7. LOEWI, O. AND NAVRATIL, E.: *Pflüger's Arch. f. d. ges. Physiol.*, 214: 689, 1926.
8. DALE, H. H. AND DUDLEY, H. W.: *J. Physiol.*, 68: 97, 1929.
9. ROSENBLUETH, A. AND SCHLOSSBERG, T.: *Am. J. Physiol.*, 97: 365, 1931.
10. LOEWI, O. AND FROELICH, A.: *Naunyn Schmiedebergs Arch.*, 62: 159, 1909.

11. LOEWI, O.: Pflüger's Arch. f. d. ges. Physiol., 237: 504, 1936.
12. GADDUM, T. H. AND SCHILD, H.: J. Physiol., 80: 9, P, 1934.
13. PAGET: Bull. Sc. Pharmacol., 37: 537, 1930.—Barker, T. H., Eastland, C. J., Everst: Biochem. J., 26, 2129, 1932.
14. CANNON, W. B. AND ROSENBLUETH, A.: Am. J. Physiol., 104: 557, 1933.
15. CANNON, W. B. AND ROSENBLUETH, A.: Autonomic neuroeffector systems. New York, MacMillan, 1937.
16. DALE, H. H.: J. Physiol., 80: 10, 1933.
17. DALE, H. H.: J. Pharmacol. & Exper. Therap., 6: 147, 1914.
18. FELDBERG, W., MINZ, B. AND TSUDZIMURA, H.: J. Physiol., 81: 286, 1934.
19. FELDBERG, W. AND GADDUM, J. H.: J. Physiol., 81: 305, 1934.
20. BROWN, G. C., DALE, H. H. AND FELDBERG, W.: J. Physiol., 81: 394, 1936.
21. ELLIOTT, T. R.: J. Physiol., 32: 401, 1905.
22. ECCLES, T. C.: Physiol. Rev., 7: 538, 1937.
23. ROSENBLUETH, A. AND SIMEONE: Ann. J. Physiol., 122: 708, 1938.
24. FORBES, A.: J. Neurophysiol., 2: 465, 1939.
25. BACQ, Z. AND BROWN, G. L.: J. Physiol., 89: 45, 1937.
26. NACHMANSOHN, D.: Yale J. Biol. & Med., 12: 565, 1940.
27. HODGKIN, A. L.: J. Physiol., 90: 211, 1937.
28. BRONK, D. W. AND BRINK, F.: Am. Rev. Physiol., 1: 385, 1939.
29. ERLANGER, T.: J. Neurophysiol., 2: 370, 1939.
30. NACHMANSOHN, D. AND COUTEAUX, R.: Proc. Soc. Exper. Biol. & Med., 43: 177, 1940.
31. SHERRINGTON, C.: Integrative action of the nervous system. London, A. Constable & Co., 1906.
32. SHERRINGTON, C.: Proc. Roy. Soc., B 97: 519, 1925.
33. NACHMANSOHN, D.: Bull. Soc. chim. biol., 21: 761, 1939.
34. MACINTOSH, F. C.: J. Physiol., 99: 436, 1941.
35. NACHMANSOHN, D.: Yale J. Biol. & Med., 12: 565, 1940.
36. LANGLEY, T. N. AND ANDERSON, K. K., J. Physiol., 31: 365, 1904.
37. LISSAK, K.: Am. J. Physiol., 125: 778, 1939.
38. DALE, H. H.: Nothnagel Vortlesung, Wien, 1935.
39. FELDBERG, W.: J. Physiol., 101: 432, 1943.
40. LOEWI, O. AND HELLAUER, H.: Pflüger's Arch. f. d. ges. Physiol., 240: 769, 1938.
41. WEISS, P. AND EDDS, M. V.: J. Neurophysiol., 8: 173, 1945

## CYSTADENOMA OF THE PANCREAS

### A CASE SUCCESSFULLY TREATED BY SURGICAL EXTIRPATION

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[From the Surgical Service of Dr. John H. Garlock]

It is with a twofold purpose that this case of cystadenoma of the pancreas successfully treated by surgical extirpation is reported and discussed: 1) to bring out certain diagnostic features and 2) to record the successful use of complete surgical removal as a therapeutic method in a disease relatively rare in medical literature.

#### CASE REPORT

*History:* F. K., (Adm. #497981), a 39 year old Polish housewife was admitted to the Second Medical Service of The Mount Sinai Hospital for the first time on October 22, 1942 complaining of a feeling of fullness in her left upper abdomen for the previous 10 months. The patient had otherwise been well except for a transient episode, 3 years previously, of nervousness and anemia associated with an enlarged thyroid gland. The feeling of fullness in her left upper abdomen had persisted until 4 months before admission, when she consulted her local physician and was told of the presence of a large "spleen" and anemia, the red blood cell count being 3,300,000. The patient was given liver therapy on which regimen she felt somewhat better, she was advised that the "spleen" was becoming smaller. This mass was examined again 2½ months before admission, and found to be much larger, and the anemia found previously still persisted. The patient was advised to enter the hospital for the purpose of establishing a diagnosis, the impression being that of Banti's syndrome.

There were no gastro-intestinal complaints, hematemesis, abnormal stools, jaundice, or weight loss. The past history was non-contributory.

*Examination:* On admission the patient was found to be a well developed and well nourished white woman with good color and in no apparent distress. The temperature was 98.6°F., the pulse rate 88, and the blood pressure 134 systolic and 70 diastolic. The eyes presented no thyrotoxic signs although the thyroid gland was diffusely enlarged. The abdomen was normal except for a firm, non-tender mass in the left upper quadrant which moved with respiration. This mass extended almost to the midline, and was palpable two fingers breadth below the costal margin in the mid-clavicular line.

*Laboratory Data:* Blood: hemoglobin, 80 per cent; red blood cells, 4,150,000; white blood cells, 8,500, with a normal differential count; sedimentation time, 50 minutes for 18 millimeters; Wassermann reaction, negative; urea nitrogen, 15 mg. per cent; sugar, 100 mg. per cent; icterus index, 5; albumin 4.3 gm. per cent; globulin, 2.4 gm. per cent; and total protein, 6.7 gm. per cent. Urine, normal. Stool guaiac test, negative. Sternal marrow aspiration, normal marrow count, and no change after the injection of epinephrine.

*Course:* There was an uneventful, afebrile course during nine days of observation, after which the patient was discharged. The discharge diagnosis was "Splenomegaly—cause unknown."

A review of the flat plate roentgenogram of the abdomen previously taken disclosed the fact that the left upper quadrant mass, which was displacing the stomach to the right, was distinct from a normal sized spleen. Because of this roentgenographic interpretation the patient was recalled for further investigation.

*Second Admission:* The patient was readmitted to the Second Medical Service on November 16, 1943 for further investigation. The physical examination and laboratory findings were similar to those found on the first admission.



Roentgenographic examination by means of a barium meal and later a pneumoperitoneum, revealed the stomach displaced to the right by a large epigastric mass. This mass was situated anteriorly, was mobile, and was independent of the gastro-intestinal tract, spleen, liver, and kidney. Intravenous pyelography disclosed incomplete visualization of the left upper urinary tract.

On the basis of the roentgenographic findings a diagnosis was made of pancreatic omental cyst and the patient was transferred to the surgical service of Dr. John Garlock for exploration. Preparatory to operation the air in the peritoneal cavity, residual from the previous studies, was removed by needle aspiration.

*Operation:* (Dr. John Garlock). Through a left upper rectus incision the peritoneal cavity was exposed revealing a globular, cystic mass the size of a grapefruit, located in the lesser sac. The transverse mesocolon was incised, permitting full visualization of the tumor. There was found a large cyst arising from the tail of the pancreas, and continuous with it. The cyst was rather firmly attached posteriorly and superiorly, the looser attachments being on the inferior surface. By means of sharp and blunt dissection, the entire mass was mobilized. In accomplishing this it was necessary to ligate branches of the splenic artery and vein. The pancreas was cut across just proximal to the cyst and the specimen removed intact. The stump of the pancreas was sewn over with silk sutures. Two cigarette drains were placed down to the lesser sac, and the mesocolon was repaired. The wound was closed in layers with wire sutures and pincets for the skin.

*Postoperative Course:* The patient had an uneventful postoperative course. The wound healed by primary union and she was discharged on the fourteenth day following operation. The microscopic report on the tumor specimen revealed a multilocular mucus cystadenoma originating in the pancreas, the wall of the cyst containing fibrous tissue and islands of Langerhans.

*Follow-up:* The patient was seen several times in the follow-up clinic, the last visit being one year after discharge, at which time she was in excellent general condition, had gained weight, and was completely asymptomatic.

*Comment.* The diagnosis of a pancreatic cyst is beset at times with many difficulties. The early signs and symptoms are by themselves not distinctive, and are similar to those associated with other intra-abdominal lesions. Whenever there appears a progressively enlarging mass in the abdomen, particularly the upper abdomen, the possibility of a pancreatic cyst must be born in mind. It is, however, a rare disease. White (1) found only 3 cases of pancreatic cyst in 6,708 autopsies at Guy's Hospital in London, England, and Judd (2) found 88 who came to operation among a total of 723,397. patients admitted to the Mayo Clinic.

It is beyond the scope of this paper to review the literature on pancreatic cysts, as this has been done very adequately by others. There are certain phases of the subject which have a bearing on the diagnostic background of the disease, and these can be profitably repeated. Boyd (3) classified pancreatic cysts as 1) retention cysts, from obstruction of the duct system of the pancreas; 2) congenital cysts, as in polycystic disease; 3) cystadenomas, the cyst wall containing pancreatic tissue; 4) and pseudo-cysts, not true cysts, but the direct result of trauma to the pancreas. The addition to this classification of 5) dermoid cyst as reported by Judd (4); and 6) cyst with carcinomatous degeneration as described by Kennard (5) and others (6), seems to complete the list.

Analysis of series of cases reveals that pain is the most common subjective symptom of a pancreatic cyst. The location of the pain varies, appearing in

any quadrant, or diffusely throughout the abdomen. The quality of the pain ranges from a sensation of fullness in the epigastrium to sharp abdominal cramps. Nausea and vomiting are frequently associated with abdominal pain. In 85 per cent of the 47 cases in the series of Judd (2), abdominal pain was a prominent part of the history. Weakness and weight loss are sometimes seen, and are usually related to cysts with malignant degeneration. There is not infrequently a past history of cholecystic disease or acute pancreatitis, but this is relatively unimportant diagnostically.

The tumor mass is characteristically hemispheric in shape, and has a smooth, tense wall. It is most commonly immobile, except when located in the tail of the organ where it is more apt to be freely movable. Judd (2), in reviewing 47 cases of pancreatic cysts, noticed that the mass generally protruded into the lesser peritoneal cavity, and was palpable above the umbilicus in 95 per cent of these cases. The position of the cyst may vary, however, and may appear in any quadrant of the abdomen, or even in the pelvis.

It is obvious from the case report that the roentgen examination is a major aid in the diagnosis of pancreatic cyst. The careful use of barium sulfate meal studies, pneumoperitoneum, and intravenous pyelography will generally clearly demonstrate the cyst. The barium sulfate enema roentgenogram may also be of help at times. In these films there appears filling defects or displacement of the stomach, duodenum, or intestinal tract. The aspiration of cyst fluid for chemical determination of pancreatic ferments is not only a dangerous procedure, but is of relatively little value, as there are numerous instances on record of true cysts in which no ferments were found.

In the differential diagnosis the following diseases must be considered: Ovarian cyst; mesenteric cyst; omental cyst; hepatic cyst; adrenal capsular cyst; cyst of the posterior gastric wall; splenic cyst; hydrops of the gall bladder; fluid tumors of the kidney; retroperitoneal tumors; and aneurysm of the abdominal aorta. Frequently the correct diagnosis can be made only through surgical exploration.

The treatment of pancreatic cysts is surgical removal in selected cases, or drainage and marsupialization in those cases not suitable for extirpation. Complete surgical removal of the tumor is frequently impossible because of adherence of the cyst to surrounding structures, and the intimate association, at times, of the splenic vein with the tumor wall (7).

#### SUMMARY

1. A case of cystadenoma of the pancreas successfully treated by surgical extirpation is reported in detail.
2. Difficulties in the diagnosis of a pancreatic cyst are illustrated by this case and a discussion of the diagnostic investigation of the disease is presented.
3. Although no review of the literature is intended, the general subject of pancreatic cysts is briefly outlined from the point of view of incidence, classification, symptoms, signs, diagnosis, and treatment.

## BIBLIOGRAPHY

1. WHITE, W. H.: Diseases of the Pancreas, Guy's Hosp. Report, 54: 17, 1897.
2. JUDD, E. S., MATSON, H., AND MAHORNER, H. R.: Pancreatic Cysts, Arch. Surg., 22: 838, 1931.
3. BOYD, W.: A Textbook of Pathology, Philadelphia, Lea & Febiger, p. 529, 1932.
4. JUDD, E. S.: Cysts of the Pancreas, Minnesota Med., 4: 75, 1921.
5. KENNARD, H. E.: Papillary Cystadenocarcinoma of the Pancreas, Surgery 9: 65, 1941.
6. RABINOVITCH, J., AND PINES, B.: Cysts of the Pancreas, Arch. Surg. 45: 727, 1942.
7. BOWERS, R. F., LORD, J. W., AND McSWAIN, B.: Cystadenomas of the Pancreas, Arch. Surg. 45: 111, 1942.

# PULMONOPLEURAL FIBROSIS SECONDARY TO PULMONARY INFARCTION

## OPERATIVE RELIEF

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*[From the Surgical Service of Dr. Harold Neuhoﬀ]*

Adhesions between the visceral and parietal pleura follow a great variety of pleuritic infections, such as empyema, pulmonary abscess and specific inflammatory diseases, and more rarely, radiotherapy and pulmonary infarction.

Extensive adhesions are maintained for long periods of time when the underlying pulmonary lesion has not subsided. Exceptionally, adhesions in the nature of pleural fibrosis may persist after the causative factor in the adjacent lung has disappeared. In the case to be reported an infarct (peripheral pulmonary embolization) had occurred months before. There was some residual fibrosis in the involved segment of the lung. The outstanding feature, however, was the extensive fibrosis in the adjacent pleura, the cause of persistent pain and the indication for an effort at operative relief.

## CASE REPORT

*History:* C. M. (Adm. #480627) a 32 year old white married male, surveyor and merchant mariner, was admitted to The Mount Sinai Hospital on October 19, 1941. Past history included an episode of fever with unconsciousness and delirium (coma?) of unknown origin in India in 1933 and operative procedure for left varicocele and hydrocele in 1928.

Three and one-half months prior to admission, patient was subjected to inguinal herniotomy at another institution. Eight days postoperatively there occurred sudden onset of right chest pain, fever, and "phlegm" without real cough (clearing of throat). Conservative treatment for pulmonary infarction was instituted; patient did relatively well. Fever subsided after five weeks, but severe chest pain and x-ray shadow (figs. 1, 2) persisted. No hemoptysis, cyanosis, dyspnea, or orthopnea at present admission.

*Examination:* Essentially negative except for a small area over the right lower chest anterolaterally where slight dullness was noted to percussion, and diminished breath sounds with few crackling râles could be heard on auscultation.

Bronchoscopy performed the day after admission under local anesthesia, was negative. Iodized oil was placed into the right middle and lower lobe bronchi. The roentgenologist reported that no pathology was visible in the bronchial tree.

Since the continued pain could be accounted for by the extensive adhesions of the infarcted lung to the parietal pleura, it was anticipated that the patient would be markedly improved by the severance of these adhesions. Accordingly, thorcotomy for the lysis of pleural adhesions was performed.

*Operation:* (Dr. Harold Neuhoﬀ). Through a long intercostal incision in the 6th right interspace, the pleural space was entered with difficulty. Extensive adhesions were present between the lower lobe and both the posterior chest wall and the diaphragm. There was a wedge-shaped old infarct in the right lower lobe over which the pleura was markedly thickened and bore massive adhesions. The adhesions were severed freeing the lung from the chest wall. Normal lung was sutured over the area of infarct infolding it and thereby burying the raw surface. The chest was closed in layers; underwater closed drainage was instituted.

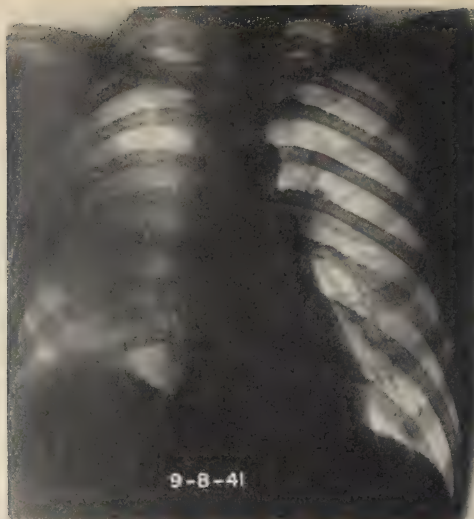


FIG. 1. Roentgenogram showing shadow of huge pulmonary infarct in right pulmonary field

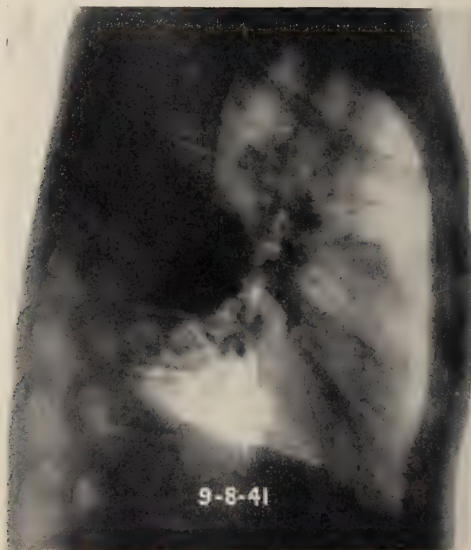


FIG. 2. Lateral view which establishes site of lesion to be in upper part of right lower lobe.



In order to further insure continued mobility of the lung free from adhesions to the chest wall, pneumothorax was attempted after operation in order to maintain the post-operative pneumothorax space which was present. A small pneumothorax pocket was present but the pressure readings became positive so quickly that continuation of the pneumothorax was thought inadvisable. Post-operative course was uneventful except for some fever. Several exploratory punctures revealed only small amounts of blood. Convalescence was satisfactory. The symptoms were greatly diminished and the patient was discharged to a convalescent home. Improvement continued until final discharge. On November 11, 1941,

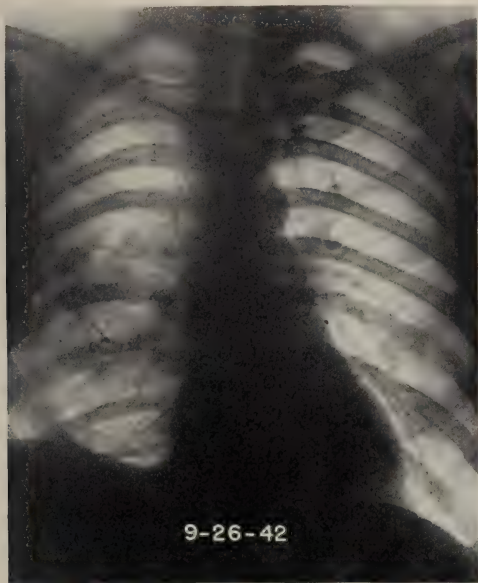


FIG. 3. Less than one year post-operatively. Essentially normal film. Note rib resection of 7th rib posteriorly.

it can be stated, the patient was asymptomatic and well. X-ray follow-up revealed the disappearance of the shadow and restitution to normal (fig. 3).

#### DISCUSSION

The pathological entity we call pulmonary infarct is well known. They, however, occur perhaps more frequently than is usually appreciated. Castleman (1), by a careful technique of blowing up the lung at post mortem and examining the specimens in conjunction with the respective roentgenograms, was able to find evidence, gross and microscopic, of many healed infarcts that would other-

wise pass unnoticed. The dimples, fissures, and septa on the surface represented chronic pleuritis covering deeper healed infarcts. "The infarct, always superficial, involves the overlying pleura resulting in localized chronic pleuritis" (1). This pleural inflammation was considered by Smith (2) to be the principal causal factor for the adhesions overlying infarcts. Warren and Giles (3), too, believe that extensive fibrous and pleural adhesions occur as a result of pleural necrosis or inflammatory reaction.

However, while adhesions occur at the site of infarction, rarely do they become thick enough to cause symptomatology and still more rarely do they persist in so doing. As far as could be determined from the literature, it is unique for a case to require surgical intervention for persistent pain due to the presence of these adhesions. In the case reported, severance of the adhesions plus re-pleuralization of the pulmonary surface permitted complete healing of the infarct, release of pleural tension, and therefore of pain.

#### CONCLUSION

A case is presented of (1) unusual sequelae to a postoperative pulmonary infarction which (2) resulted in massive intrapleural adhesions requiring (3) surgical release resulting in (4) complete cure of symptoms as well as (5) clearing of pathology as depicted by X-ray films.

#### BIBLIOGRAPHY

1. B. CASTLEMAN: Arch. Path., 30: 130, 1940.
2. E. B. SMITH: Arch. Path., 35: 553, 1943.
3. S. WARREN AND O. GATES: Arch. Path., 30: 440, 1940.

# PENICILLIN THERAPY IN A CASE OF CHRONIC SUPPURATIVE BRONCHIECTASIS

LOUIS E. SILTZBACH, M.D.<sup>1</sup>

## CASE REPORT

*History:* The patient, aged 61 years, became ill in January, 1942 when he developed coryza followed by fever, malaise, cough and expectoration of large quantities of greenish, odorless sputum. His family physician detected signs of pneumonia in the left lower lobe and sulfathiazole was administered. There was no response to the drug and he was admitted to a hospital on the twelfth day of his illness. There, he had a daily rise in temperature to 104°F. and a chest roentgenogram revealed infiltrations at the left base with a triangular area of density behind the heart. The latter was thought to represent an encapsulated empyema. Thoracentesis yielded but one cc. of thick yellow pus. Thoracotomy with rib resection was performed on the fifth hospital day but an uninvolved pleural space was found. Following operation, high fever continued and another chest roentgenogram disclosed that the right lower lobe contained areas of pneumonic consolidation as well. Sulfadiazine therapy was again instituted with no effect upon the fever nor upon the quantity of purulent sputum which now amounted to from 180 cc. to 240 cc. daily. Because of the persistence of the shadow behind the heart, another thoracentesis was performed and, again, only one cc. of thick pus was obtained. This yielded non-hemolytic *Streptococci* on culture. It was felt that the aspirating needle had entered the lung on both attempts.

Subsequently, a bronchogram showed marked saccular bronchiectasis of the left lower lobe bronchi and the patient was put on postural drainage. There was no improvement. He continued to have low-grade fever and was transferred to a hospital for chronic care after fifteen weeks' stay.

At the second hospital, he was confined to bed for five months. His chest roentgenograms showed slow resorption of the right lower lobe infiltrations but the density behind the heart persisted. The cough was intractable and the sputum became foetid and occasionally blood-streaked. Nonetheless, his temperature became normal, he gained some weight and was finally sent to a convalescent farm and later, to Phoenix, Arizona where he remained for one year. While there, he had an episode of massive hemoptysis, expectorating about 500 cc. of blood. He returned to New York City in April, 1944 because of a harassing cough, the persistence of foetid sputum amounting to 120 cc. to 180 cc. daily, and because of his desire for surgical treatment. This brought him to The Mount Sinai Hospital Chest Clinic in June, 1944.

Here, his general condition was found to be fairly good, his blood pressure was 216 systolic and 110 diastolic (the patient had known of his hypertension for twenty years) and his electrocardiogram showed evidence of myocardial damage. A chest roentgenogram showed a shrunken left lower lobe. Bronchography revealed saccular bronchiectasis of the left lower lobe bronchi and a normal pattern in the right lower lobe (fig. 1). Bronchoscopy revealed large quantities of foetid muco-pus coming from all branches of the left lower lobe. The mucosa was thickened and bled easily and a biopsy revealed acute and chronic inflammatory changes. Sputum cultures revealed a mixed flora containing *Streptococcus viridans*, *Micrococcus catarrhalis* and *pharyngis siccus*, *Staphylococcus albus* B. and *E. coli*. The amount of sputum was measured daily and was found to vary between 120 cc. and 180 cc. for a twenty-four hour period.

Briefly, then, we were dealing with a patient who had had suppurative bronchopneumonia

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<sup>1</sup> From the Group for Thoracic Diseases and the Medical Department of The Mount Sinai Hospital. Presented at the monthly conference of the Group for Thoracic Diseases, November 6, 1944.

two and one-half years previously which had left in its wake a shrunken, bronchiectatic left lower lobe causing symptoms which totally incapacitated him. Because of the patient's age and his cardiovascular difficulty, he was considered too poor a risk for lobectomy and a trial of penicillin therapy in the hospital was decided upon.

*Penicillin Therapy.* On August 26, 1944, 15,000 units of penicillin was injected intramuscularly every three hours. This resulted in a blood level of 0.4 unit per cc. of serum, one hour after injection. By the third day of intramuscular therapy, the sputum quantity



FIG. 1. Penicillin therapy in a case of chronic suppuration bronchiectasis

was reduced to 30 cc. for twenty-four hours. On this day, after preliminary postural drainage, 10,000 units of penicillin dissolved in 100 cc. of normal saline was instilled into the left lower lobe by means of a soft rubber catheter. This was introduced under fluoroscopic control after cocainization of the larynx. The patient was then placed in a sitting position in bed leaning toward the left and was cautioned against coughing for the next two hours. There were no signs of bronchial irritation following the instillation. Twenty-three hours after the instillation, only a small amount of odorless sputum could be obtained and this showed the presence of 0.4 unit of penicillin per cc. of sputum. The instillations were given daily and the dose was increased to 25,000 units in 100 cc. of normal saline, a concentration of 250 units per cc. After the second intrabronchial instillation and on the seventh day of the intramuscular course, no more sputum was obtainable. The patient lost his cough

and his sleep was undisturbed for the first time since the onset of his illness. Both routes of therapy were continued for five days and then, after nine days, the intramuscular injections were discontinued and only the instillations were carried out. Eleven instillations were given in all. In summary, he received four days of intramuscular injections, five days of combined therapy and six days of local treatment alone. In units, this amounted to 800,000 intramuscularly and 260,000 intrabronchially, a total of 1,060,000 units. One other figure is significant. One hour after the intrabronchial instillation of 25,000 units of penicillin, a blood sample showed a concentration of 0.13 unit per cc. of serum, indicating that the drug was being absorbed from the lung.

The patient has now been observed for eight weeks since the discontinuation of the penicillin therapy and there has been no recurrence of symptoms. He has had one attack of coryza followed by cough during the fifth week following treatment. During it, he expectorated less than one dram of mucoid sputum during the six days that it lasted. He has no cough or expectoration at present and he is now ready to return to work.<sup>2</sup>

*Comment:* By means of combined intrabronchial and intramuscular penicillin therapy, remission of symptoms has been achieved in a case of chronic suppurative bronchiectasis. The period of observation is too short to indicate the lasting value of the therapy. The risk of recurrence is not removed; for although the bronchopulmonary infection was apparently controlled, the anatomic deformity of the bronchi, as demonstrated by subsequent bronchography, persists. However, even if the remission prove fleeting it would still suggest that repetition of such a course of therapy may serve to keep relatively comfortable those patients who are not suitable for lobectomy. Penicillin therapy may also prove helpful as a preliminary measure to lobectomy by rendering the patient "drier" and thus reducing the hazard of bronchogenous spillover infection during and after operation.

Studies are in progress to determine the importance of such factors as route of administration, dosage, concentration of drug, and frequency of treatment, as well as the effects of therapy upon the bacterial flora of the respiratory tract.

<sup>2</sup> Follow-up observation eight months after completion of therapy showed no recurrence of symptoms in spite of a rather severe upper respiratory tract infection. He is working full time.



# ESSAYS ON BIOLOGY OF DISEASE<sup>1</sup>

ELI MOSCHCOWITZ, M.D.

## CHAPTER 9

### THE BIOLOGY OF GRAVES' DISEASE

The diagnosis of Graves' disease is obvious when the classical quadrad of signs, namely tremor, tachycardia, swelling of the thyroid gland and exophthalmos, are present. Difficulty enters into the strict nosological status of the exceedingly common group of patients who present the characteristic neuropathy but in whom one or more of this quadrad of signs are absent. For instance, exophthalmos is missing in about one quarter of the cases (23.2 per cent-Sattler) (1) and in about the same proportion there may be no swelling of the thyroid gland. Even a tachycardia of appreciable degree may be absent, and a tremor is by no means constant. While such patients are usually sensitive, emotional, overstimulated, anxious, irritable and reveal great swings between ecstacy and depression, even this neuropathic personality may not be prominent, constituting rare cases of the so-called "apathetic" types of Graves' disease. In my experience however, the apathy is more apparent than real, and on deeper analysis the apathy is found to be a mask rather than a state of mind.

These abortive cases have received different names in the past; *formes frustes*, autonomic imbalance (2), Basedowid (3), pre-Basedow (4), and neurocirculatory asthenia. Between this primitive type and the complete end product comprising the quadrad of cardinal signs, one finds an endless variety of clinical combinations: tachycardia, tremor and enlarged thyroid gland without exophthalmos; tachycardia, tremor and exophthalmus without an enlarged thyroid; tremor and tachycardia without exophthalmos or an enlarged thyroid gland, etc. Most observers have been unwilling to classify these larval forms within the domain of Graves' disease, unless the basal metabolic rate is elevated. Such a conclusion is based upon a static rather than the dynamic or biological viewpoint of disease processes and has created a number of fallacies.

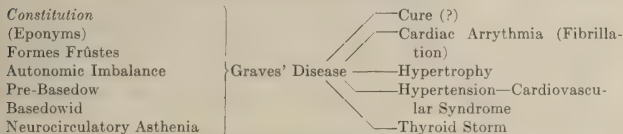
1. It is fallacious to believe that the symptom complex at the time when it was observed had attained its fullest fruition, and was not merely a phase of a process whose natural history extended long before and projected long after the period of observation. I have had the fortunate experience of witnessing the development of classic Graves' disease in a number of patients whom I have watched closely for many years previously. These were sensitive, sanguine, quick, overstimulated, introvert, emotionally unstable folk and possessed a temperament that I

<sup>1</sup> This is the ninth chapter in a series of essays by Dr. Eli Moschcowitz, in which an attempt will be made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. When the publication of the projected series of essays is completed, the several installments will be assembled and printed as a monograph.—Ed.

have called "allergic to life." They reveal a strong manic depressive life curve. They often give a history of "nervous diarrhea." These attributes are usually traceable back into childhood. The eyes were bright and under emotional stimuli, the pulse became rapid, tremor developed, they flushed easily and the eyes became starey. If the emotional insult continues, these manifestations lost much of their lability and became more or less fixed. The basal metabolic rate at this time while within the range of normal, veers to the plus side. If the emotional insult is profound or protracted, one witnesses the process of hyperkinesis (5) with an exaggeration and greater fixation of these signs. The tremor and tachycardia persist, the eyes become exophthalmic, the thyroid may begin to swell and the basal metabolic rate attains abnormal levels. Soon weight loss and excessive sweating ensue, and the clinical picture of Graves' disease is then complete.

# BIOLOGY OF GRAVES' DISEASE



The type personality I have described plus the individuals reaction to the environment represents the constitutional factor in Graves' disease that has been emphasized repeatedly (6-9) and differs in no way from that implied in the terms *formes frustes*, autonomic imbalance, Basedowid, pre-Basedow, and certain instances of neurocirculatory asthenia.<sup>2</sup>

Opinions are various as to whether this constitution is congenital or acquired, but Lorand and Moschcowitz (10) have submitted strong evidence that it is largely conditioned by environmental factors, in which parental overprotection plays by far the dominant role. There is little ground for assuming that anatomical characters form part of the constitution. There is no particular physical conformation that is prone to acquire Graves' disease. The very frequent association of status thymico-lymphaticus and Graves' disease, has afforded to some, especially Warthin (11) grounds for holding that anatomical characters partake in this constitution. I have discussed this relationship (12) and have submitted evidence that indicates that the status thymico-lymphaticus represents one of the backgrounds that notoriously renders the patient extraordinarily sensitive to both physical and emotional stimuli.

2. It is fallacious to believe that the measurement of the basal metabolic rate constitutes a decisive differential between Graves' disease and the abortive forms represented under the terms autonomic imbalance, etc. Inasmuch as the basal

<sup>2</sup> Bernstein and I have adduced strong evidence that most cases of neurocirculatory asthenia are the larval phase of Graves' disease. Among other evidence, we cite 12 cases observed in The Mount Sinai Hospital, in which on the first admission the diagnosis of neurocirculatory asthenia was made and on a subsequent admission, Graves' disease.

metabolic rate measures in part at least, the degree of thyroid activity, the term "hyperthyroidism" is conventionally regarded as synonymous with Graves' disease. I believe this is entirely arbitrary and unwarranted and has tended to perpetuate other current subsidiary fallacies regarding the nosology of Graves' disease. My reasons for this viewpoint are the following:

a. Administration of active thyroid preparations even over a prolonged period mimics but never completely reproduces the clinical picture of Graves' disease (13);

b. After thyroidectomy the basal metabolic rate usually drops to normal but many of the cardinal evidences of Graves' disease may persist, often permanently. The one factor that always remains is the underlying personality or constitution, which is always potential to flare up into the active stage of the disease, given the proper environment. Under such circumstances, the diagnosis assuredly does not change because the basal metabolic rate has returned to normal.

c. Most clinicians are familiar with so-called "spent" cases of Graves' disease, i.e. patients who reveal all the clinical evidences of the disease, although the basal metabolic rate is within the normal range. This, of course, does not imply that at some previous stage, the basal metabolic rate had not been elevated; it probably was, but in diagnosis one can only be concerned with data obtained at the time of observation.

On a priori grounds, it is unreasonable to expect that the basal metabolic rate can be a decisive differential, because the range between which the rate  $+15$  to  $-15$  is regarded as within the normal is entirely arbitrary. For purposes of diagnosis, the determination of the basal metabolic rate has precisely the same value as thermometry in febrile disorders. It is entirely a measurement of activity and more particularly of the hyperthyroid component in the totality of the clinical expression. Graves' disease may therefore be represented in the following equation:

Constitution + hyperthyroidism = Graves' disease. Being therefore a hyperkinetic disease, the diagnosis of Graves' disease cannot depend upon a specific test such as for example the finding of tubercle bacillus in suspected tuberculosis, but on a study or reconstruction of the total organ-personality. The history in a patient with Graves' disease, therefore, does not begin with the onset of the signs and symptoms, but at birth, and should comprise the story of all the parental, familial, social, economic and sexual influences; his loves, his hates, and the fears, to which the patient has been subject.

There are many who hold that the diagnosis of Graves' disease can only be established by finding the characteristic hyperplasia of the thyroid gland. This can hardly be valid, because such a hyperplasia is absent in about 10 to 15 per cent of the cases (14-16).

The biology of Graves' disease, however, does not culminate when the transition from the larval or constitutional phase to the fully developed form has been attained. Henceforth its possible evolutions, if the progress of the malady is not checked, are various.

1. As a result of the persistent tachycardia and the consequent increase in

volume output, the heart hypertrophies. In time left ventricular failure ensues and eventually failure of the right heart with hypertension of the pulmonary circuit (see Chapter 1).

2. An arrhythmia develops, nearly always auricular fibrillation, again with the sequence of left and right ventricular failure.

3. Hypertension ensues. This eventuality is especially common in patients within the older group, but it is by no means uncommon in younger patients, masking in the form of "diencephalic" hypertension (17). In a number of instances, I have had the opportunity of witnessing the development of hypertension in patients with "spent" Graves' disease. As a result of the high pulse pressure characteristic of Graves' disease with a comparatively low diastolic pressure, there is at first a compensating rise in systolic pressure. In time the diastolic pressure also rises, and as the process continues, both systolic and diastolic pressures rise to real hypertension levels. Eventually, usually after many years, the cardiovascular syndrome develops precisely similar to that described in hypertension of the greater circulation (see Chapter 2.)

4. Thyroid storm. This may occur either spontaneously or after operation. Fortunately, with the introduction of Lugolization this tragic eventuality occurs less frequently than before.

5. Certain mild cases pursue what apparently appears a favorable course upon, what some writers term, "skillful neglect." The pulse slows, the tremor subsides, the basal metabolic rate returns to normal levels, and the patient returns to a social and economic adjustment. But the psyche or in other words, their constitution remains, which henceforth usually reacts like a hairtrigger to the buffetings of their environment; they remain unstable, anxious, develop tremor and tachycardia under the slightest provocation, and in an appreciable number of instances, if the provocation is intense and prolonged, develop a genuine Graves' disease. It is reasonable to infer that temporarily these patients have lost the hyperthyroid component.<sup>3</sup>

The identical sequence of events occurs after subtotal thyroidectomy. The operation, so to speak, amputates the hyperthyroid component. The reduction of the basal metabolic rate accomplishes much by reducing or even eliminating many of the hyperkinetic phenomena. The tremor and tachycardia subside, the excessive sweating and agitation is reduced, the weight begins to rise, a peaceful sleep is restored. But the underlying psyche or constitution remains, again potential, given the proper environment, to bring forth a recurrence. A patient with Graves' disease is never completely cured in the sense that one cannot predict with any assurance that a recurrence will never take place. For this reason, as we have previously insisted, the treatment of the patient with Graves' disease only begins when the operation has been finished.

Often enough, and especially if the disease is protracted, the operation may

<sup>3</sup> It is well to be reminded that of the total metabolism the thyroid gland contributes only 40 per cent (18). To what extent the basal metabolic rate in Graves' disease represents thyroid activity alone or is derived from the total metabolism can only be determined by total thyroidectomy, an operation which is not generally done in this disease.

only reduce the hyperkinetic phenomena to a lower order of activity; tremor and tachycardia are lessened, the basal metabolic rate hovers around the upper limit of the normal or even slightly higher, sweating continues and the weight remains stationary. They remain "nervous" anxious and fearful. In other words, the cycle reverts itself. A number have been reported (19, 20, 21) as having developed the complication (?) "neurocirculatory asthenia." If a true recurrence of Graves' disease does not occur, some develop the cardiac or cardiovascular sequelae outlined in 1, 2 and 3. This statement is based not only from direct observation for a sufficiently long period in a few instances, but also by reconstruction of the life history in certain patients with cardiac disease, the origin of which seemed obscure.

To summarize, Graves' disease is a psychosomatic disease and its clinical expression represents a hyperkinesis of many normal bodily functions, the dominant one being the normal basal metabolic rate. The background is a constitution mostly psychic in makeup largely conditioned by environmental factors, and the disease attains its fullest fruition usually as a result of either a catastrophic or a prolonged psychic strain. Between the background and the fully developed form occur a host of clinical expressions that have received different eponyms in the past. These merge into themselves so imperceptibly that it is sometimes extremely difficult to determine when the disease begins and when the constitution ends, and it is only by a study or a reconstruction of the total organ-personality together with an adequately prolonged follow-up that the biology of the disease can be recognized. By so doing, the biological course will be found to be in both directions, sometimes forward toward hyperkinesis and sometimes the reverse, toward regression, depending upon the individual's reaction to his environment.

#### BIBLIOGRAPHY

1. SATTLER: Die Basedowische Krankheit, Leipzig, 1910.
2. HYMAN AND KESSEL: J. A. M. A. 85: 1017, 1925.
3. STERN: Jahrb. Psychiat. u. Neurol. 39: 180, 1909.
4. ZONDEK AND BANSI: Klin. Wehnschr. 8: 1697, 1929.
5. MOSCHCOWITZ: Am. J. M. Sc. 206: 576, 1943.
6. CHARCOT: quoted by Chvostek: Morbus Basedow und die Hyperthyreosen, Berlin, 1917.
7. KOCHER: Arch. f. klin. Chir. 92: 677, 1910.
8. Chvostek: Morbus Basedow und die Hyperthyreosen, Berlin, 1921.
9. BAUER: Die Konstitutionelle Disposition zu inneren Krankheiten, Berlin, 1921.
10. LORAND AND MOSCHCOWITZ: J. Nerv. & Ment. Dis. 79: 136, 1934.
11. WARTHIN: Ann. Int. Med. 553, 1928.
12. MOSCHCOWITZ: Arch. Int. Med. 553, 1928.
13. MCCARRISON: Proc. New York Path. Soc. 21: 154, 1921.
14. HOLZWEISSIG: Deutsche Ztschr. f. Chir. 193: 276, 1925.
15. SIMMONDS: Virchow's Arch. f. path. Anat. 211: 73, 1913.
16. KLOSE AND HELLWIG: Arch. f. klin. Chir. 128: 175, 1924.
17. PAGE: Am. J. M. Sc. 190: 9, 1935.
18. MEANS: Thyroid and its Diseases, Philadelphia, J. B. Lippincott Co., 1937.
19. PRIOLEAU: Ann. Surg. 109: 729, 1939.
20. CLUTE: Ann. Surg. 106: 2, 1929.
21. SPENCE: St. Barth. Hosp. Gaz. 43: 189, 1936.
22. MOSCHCOWITZ AND BERNSTEIN: Am. Heart J. 23: 177, 1944.



## LIFE'S LATER YEARS

### STUDIES IN THE MEDICAL HISTORY OF OLD AGE

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#### PART 8<sup>1</sup>

#### THE REVIVAL OF LEARNING

(1483-1600 A.D.)

*"But if phisitions be angry, that I have wryten phislike in englyshe, let theym remember, that the Greeks wrote in greek, the Romanes in latyne, Avicenna, and the other in Arabike, which were theyr owne propre and maternal tonges. And if they had bene as moche attached with envy and covaytise, as some nowe seeme to be, they wolde have devysed somme particular language, with a strange syphre or forme of lettres wherein they wolde have writen their science, which language or lettres no man shoulde have knowen that had not possessed and practised phisycke; but those, altho they were painimes and Jewes, in this parte of charity they farre surmountid us Christianes, that they wolde not have soo necessary a knowledge as phisicke is to be hyd from them, whych wolde be studiouse aboute it."*

*Sir Thomas Elyot-Castel of Helth (1541).*

As we slowly pick our way through medical history, pausing here and there to dwell upon the work and opinions of men who have left behind evidence of their interest in our problem, let us not neglect the main stream of medical progress, upon which in every epoch the advancement of the knowledge of old age has necessarily depended. The contributions of each period to a special field are made strictly in accordance with its general medical understanding. At no time has the topic of old age been actually neglected, as many professional and lay writers seem to think, but the quality of the thought and the amount of attention given to it, have varied widely.

We have observed at times during the preceding centuries individual efforts toward original thinking. These availed but little to loosen the bondage in which the Arabs and their medieval followers were held by the anatomy and physiology of Galen, verbosely reinterpreted through 10 or 12 centuries. With the fall of Constantinople in 1453, the first scholars came to Italy who could read and interpret the medical classics in the original Greek. As late as 1499, when Erasmus went to Oxford, he could find there no teacher of Greek, and the following year in Paris received only imperfect instruction.

<sup>1</sup> This is the eighth in a series of articles dealing with Studies in the Medical History of Old Age. Upon completion of their publication, the installments will be collected and reprinted in a single volume, constituting one of the Series of Monographs of The Mount Sinai Hospital Press.—Ed.

The forces of independent inquiry released by the revival of learning had profound effects on medicine. On every side, in Italy, later in France, Germany and England, men rose up to protest against scholasticism and superstition, to substitute direct observation for hair-splitting dialectic. The anatomical studies of the renowned artist Leonardo da Vinci (1452–1519) paved the way for the revolutionary anatomical teaching of Andreas Vesalius (1514–1564), whose *De Fabrica Humanis Corporis* (published at the age of 28) with the vivid and accurate illustrations of Jan Kalkar, was concerned with function as well as structure, with pathological as well as normal anatomy. This work is properly regarded as the foundation of modern medical thought. Fabricius of Aquapendente, a student of Vesalius, was the teacher of William Harvey and the inspiration of his immortal discovery.

The vernacular version of *De Fabrica* prepared by Ambrose Pare (1510–1590) had a wide influence on the surgery of the Renaissance and illustrates the growing tendency to substitute the mother tongue for the Latin of the university scholars. The controversy over this question is bluntly terminated by Sir Thomas Elyot in the passage which stands as epigraph to this chapter. During this period several famous old books on old age appeared for the first time in English. Arnold of Villanova's work *De Conservatio juventutis et retardationis senectutis* first appeared in English in Drummond's translation in 1544; Paynel's *Regimen Sanitatis Salerni* in 1528; Baker's version of Gesner's *The New Jewel of Health* in 1576; and Ward's translation of the French edition of Alexis of Piedmont's *Secrets* in 1560.

The last two works indicate clearly the persistence of superstition and folk medicine in spite of the enlightenment of the times. Although sometimes listed in bibliographies of the medical history of old age, neither of the works constitutes anything more than background for the development of our theme, as is apparent from the title-pages.

*"The Secretes of the Reverende Master Alexis of Piedmont containing many excellent Remedies agaynst dyvers diseases, woundes, and other accidents, with the manner to make distillations, parfumes, confitures, dyings, colours fusions and meltynges. A work wel approved verye profitable and necessary for everyman. Translated out of Frenche into Englishe by William Warde, 1559."*

*"The newe Jewel of Health wherein is contained the most excellent of Secretes of Phisicke and Philosophie, divided into fower bookes. In the which are the best approved remedies for the disease as well as inwarde as outwarde, of all the partes of the mans bodie: treating very amply of all distillations of Waters, of Oyles, Balmes, Quintessences, with the extraction of artificial salts, the use and preparation of Antimony and Potable Gold. Gathered out of the best and most approved authors by that excellent Doctor Gesnesrus. Also the pictures, and manner to make the Vessels, Farmaces, and other instruments thereunto belonging, Faithfully corrected and published in Englysh by George Baker, Chirurgien."*

Conrad Gesner (1515-1565) to whom this book is ascribed, was a master of botany, zoology and medicine. He wrote copiously on all branches of human knowledge, including Alpine scenery and mountain climbing. One cannot but wonder his thoughts on reading his translator's dedication of his work to the Count and Countess of Oxford in which he says that "this newe Jewell wyll make the blynde to see, and the lame to walk. This newe Jewell will make weake to become strong, and the olde crooked age to become lustye. This newe Jewell will make the soule seeme beautifull, and the withered face seeme smoothe and fayre, yea, it will heal infirmities and all paynes in the bodie of man." Among the remedies offered to work these wonders is one strangely reminiscent of the Smith Papyrus. "An Oyle of Myrre, that mayntaineth the person long youthfull even as the naturall balme doth; for this oyle by his naturall virtue defendeth and preserveth all things from putrefying, which are layd into it; and this also anointed on the face, mayntaineth a freshe and comely face; and that youthful appearing."

Ranked by Garrison with Vesalius and Pare, as one of the three great medical leaders of the sixteenth century, is Aureolus Theophrastus Bombastus von Hohenheim (1493-1541), the self-styled Paracelsus, whose turbulent life and truculent teachings generated controversies in his own time which have prevented until recently his proper evaluation. While schooled in the classics, Hippocrates and Aristotle, he publicly burned the works of Galen and Avicenna. Lecturing in German he declared himself greater than the highly respected Celsus. His writings are everywhere permeated by alchemical therapeutics, but established in practical use such drugs as opium, mercury, lead, sulphate, iron, arsenic, copper sulphate and potassium sulphate. The mixture of mysticism and ranting with sound observation and studied experience in his writings render their interpretation most difficult.

The subject of long life was an important feature of all discussions of the Hermetic Mysteries. The following passage from Paracelsus represents the master "in his most arcane manner", to quote Waite, the translator and editor of the authoritative works (1).

*"There have been other men, indeed, not unworthy of mention, who surpassed the ordinary length of life. As Moses, who completed 120 years, yet not according to the method of magic, but rather of physical life, to whom was joined so strong a nature that it attained a great age without difficulty. Like instances occur in our days, and will be found occasionally to the end of the world. Some, again, by the help of magic, have lived to a century and a half, and yet some have attained to a life of several centuries, and that by the adjoined force of Nature, which exists fully in metals and in other things which they call minerals. This force lifts up and preserves the body above its complexion and inborn quality. Of this kind are the Tincture and the Stone of the Philosophers because they are elicited from antimony, and, similarly, the quintessence. These and other numerous arcana of the Spagyric Art are met with, which in all manners restore the body exhausted by age, returns it to its former youth, and free it from all sickness, a fact which is well known to all acquainted with this monarchia."*

A similar confusion of thought, a mixture of what to us seems sense and non-sense is found in other eminent writers of this period. Erasmus (1467–1536), the famous Dutch scholar and humanist, combined learning, stylistic brilliance, humor and tolerance. In his *Praise of Medicine* (2) there occurs a striking



FIG. 1. Marsilius Ficinus (1433–1499). (From print in the collection of The Home for Aged and Infirm Hebrews, N. Y.).

passage quoted by Schwalbe in the Introduction to his *Lehrbuch der Greisenkrankheiten* (1907). "A heavy burden is old age, which can no more be eluded than death itself. But medical aid is often able to postpone its onset and to palliate its maladies in a striking fashion." By itself this is an impressive statement, but taken in its context, the words assume an entirely different significance, as Erasmus continues: "For it is no fable, but vouched for by several witnesses, that man by means of the so-called Fifth Essence can strip off senile weakness like a

snake skin, and be rejuvenated." This Fifth Essence was the creation of Raymond Lully (1234-1315), the alchemist, and discussed in his *Libellus de secretis naturae*, Augsburg, 1518, where it is ascribed every imaginable power over disease, old age and death, as well as over minerals and plants.

Knowledge mixed with credulity and superstition are manifest in the work of Marsilius Ficinus the Florentine (1433-1499), noted as the translator of Plato into Latin and as a protege of Cosimo da Medici. His *De triplici vita*, privately printed at Basle not later than 1498, contains three books, *De Vita Sana*, *De Vita Longa* and *De Vita Coelitus Comparandi*. A German translation of the first two books, *Das Buch der Gesundheit*, was printed in Strassburg in 1505. That Ficinus followed the Arab pattern in his work is clear from the following chapter headings. "The first chapter says that for a perfection of art and the learning of wisdom a long life is necessary which is to be desired and guarded." "The second chapter shows that the bodily heat and warmth is diminished by dampness." "The third chapter teaches how to preserve the warmth and heat of the body against moisture, as Minerva the goddess of wisdom advises." "The sixth chapter tells the common rules for eating and drinking, and the nature of foods and clothing." "The fourteenth and last chapter teaches how to avoid and prevent the serious accidents and injuries." He advised consultation with an astrologer every seventh year to find out what dangers threatened and resort to a physician to learn how to prevent the impending trouble. He recommended to old people the internal use of gold, frankincense and myrrh, since the wise men offered these three to the Creator of the stars in order to obtain from him the favorable influence of the three lords of the planets, Sol, Jupiter and Saturn.

Contrasting with Ficinus, is his contemporary, Gabriele Zerbi (1468-1505), celebrated as professor of anatomy at Padua, whose anatomic treatise published in 1502, was the first to separate organs into systems. Zerbi's book on old age (3), dedicated to Pope Innocent VIII, has never received the attention from medical historians that its rich content deserves. Thanks to the erudition of a friendly scholar, an abstract of this little known work has been made available (4). In it we find a wealth of practical information on the hygiene of old age, with a general similarity in form and content to Arab works of the preceding centuries. The preoccupation with astrology as shown in Ficinus is here also evident. In dividing old age into two periods, Zerbi describes first, "latent old age" ranging from thirty to sixty years, which is under the influence of the planet Jupiter, and second, "manifest old age," which is under the influence of Saturn. It is emphasized that there is no life extension beyond the natural limit of life and that gerontocomia should aim at retardation only. It is a special art consisting of conservative and preservative measures, and the use of the six "res naturales." The master of this art is a specialist in old age, and is called "gerontocomus" by the author. His qualifications and duties, as well as those of his assistants are described in detail. The best locations and climates for residences for the aged are discussed. The greater part of the book, Chapters 16 to 56, contain rules for exercise, bathing, rest, eating and drinking, sleeping, evacuations, and mental health. Among the therapeutic agents are viper meat, and



broth, distillate of human blood, gold solutions, as well as rare stones and syrups for the retardation of old age. Sex hygiene and conservation of sight and smell are among other topics thoroughly discussed. In general this is a highly worthwhile, conscientious effort to elucidate the subject, and should be placed high among the works of Renaissance physicians on old age.

Antonius Fumariellus Veronensis wrote *De seniam regimine, anno 1540*, in which, according to MacKenzie, he declares that he "follows the sentiments of Hippocrates and Galen." Another Italian of this period was Tommaso Rangoni, known by his pen name of Thomas Philologus Ravenna. His *De Vita Hominis ultra CXX annos protrahenda* was addressed in 1553 to Pope Julius III. He is said to be the first physician to criticize the custom of having public burying places in populous cities because they contaminate the atmosphere and frequently spread fatal diseases.

In 1534 in England, Sir Thomas Elyot published *The Castel of Helth*. The first edition, of which no copy is known, is said to have been dedicated to Thomas Cromwell (see Bull. New York Acad. Med., 5:1, January, 1929). This fascinating nobleman had many interests, including political philosophy and the theory of education as well as medicine, in which by his own account he was extremely well read. Limited in actual medical experience he brought to the old established authorities a strong admixture of good sense and a forceful style. His book is devoted almost entirely to dietetics as then understood and as had been practiced for many centuries.

*"Always remember, that aged man shuld eate often; and but litel at every time, for it fareth by them as it doth by a lampe, the lyght whereof is almost extincite, which by pouring oyle and litel is long kept bourninge: and with moch oyle poured in at once, it is clene put out."*

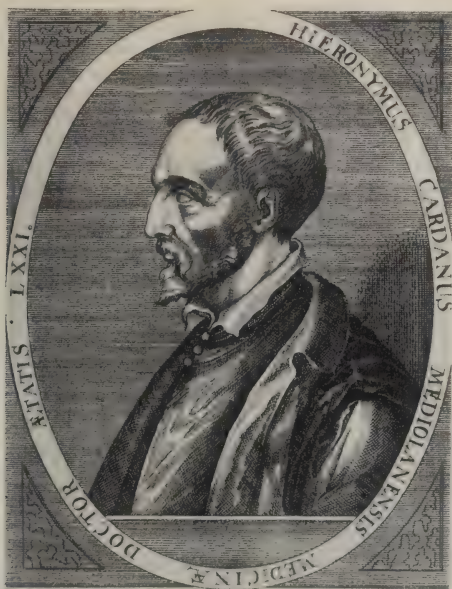
His list of "syckenesses of age" is reminiscent of Hippocrates' famous Aphorism.

*"Difficultie of breth, reumes with coughes, strangulyon, and difficultie in pyssynge, ache in the ioyntes, diseases of the raynes, swymmynges in the head, palseyes, ytchyng of all the bodye, lacke of slepe, moysture in the eyes and eares, dulnesse of syght, hardnesse of hearynge,—or shortnesse of breth. Although many of the said sycknesses do happem in every tyme and age: yet because they be most frequent in the sayde tymes and ages I have written them, to the intent, that in the ages and tymes moste inclyned unto them, such thinges mought be than eschewed, which are as aptte to ingendre sayde dyseases."*

Not the least of Sir Thomas' charm is his spelling. His work ran into at least three editions, and had a wide influence among the people, if not among the profession.

*The old mans dietarie* (5) of Thomas Newton, published in 1586, is noteworthy chiefly as a medical work that was current in Shakespeare's day. In it we find Elyot quoted very freely, sometimes with credit, but as often not.

An eighteenth century work, the *History of Health*, by MacKenzie contains references to works of old authors, which are not to be found in present day bibliographies. Among these writers is Ferdinandus Eustachius, son of the famous anatomist Bartholomaeus Eustachius, who in 1589 wrote *De vitae humanae a facillate medica prorogatione*, and dedicated it to Pope Sixtus V. In it



CARDANUS hic pupus dicitur esse Magnus:  
 Per uerum uerum BENEDICTVS est

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FIG. 2. Jerome Cardan (1501-1576). (From print in the collection of The Home for Aged and Infirm Hebrews, N. Y.).

he refutes many arguments alleged to prove that the medical art is of no use in prolonging life, but, as Mackenzie points out, is silent as to the means by which that end may be attained.

We come now to the fascinating figure of Jerome Cardan (1501-1576) who practiced in Milan and served as professor of medicine at Pavia and Bologna. His fame today rests on his mathematical work and on his contributions to physics, especially his efforts to measure the density of air. In his own time he

was so highly regarded as a practitioner that he travelled to Edinburgh from Italy for consultation on the illness of the Archbishop Hamilton. Two medical works on old age are known (6), but among his many literary productions, his autobiography, *The Book of My Life*, stands out in the opinions of scholars as the first of the great introspective studies of a man's inner being. In it as well as in his essay *De Utilitate* are many bitter references to old age. According to Waters (7), Cardan declares old age to be the most cruel and irreparable evil with which man is cursed, and to talk of old age is to talk of the crowning misfortune of humanity. Old men are made wretched by avarice, by dejection and by terror. He bids men not to be deceived by the flowery words of Cicero when he describes Cato as an old man, like to a fair statue by Polycleitus, with faculties unimpaired and memory fresh and green. He next goes on to catalogue the numerous vices and deformities of old age, and instances from Aristotle what he considers to be the worst of all misfortunes, to wit, that an old man is well-nigh cut off from hope; and by way of comment, grimly adds, "If any man be plagued by the ills of old age he should blame no one but himself, for it is by his own choice that his life has run on so long." Cardan, as Waters points out, offers a few words of counsel as to how this hateful season may be robbed of some of its horror. Our bodies grow old first, then our senses, and last our minds. Therefore let us store our treasures in that part of us that will hold out the longest, as men in a beleaguered city are wont to collect their resources in the citadel, which albeit it must in the end be taken, will nevertheless be the last to fall into the foeman's hands. Old men should avoid society, seeing that they bring nothing thereto worth having; whether they speak or keep silent, they are in the way, and they are as irksome to themselves when they are silent as they are to others when they speak. The old man should take a lesson from the lower animals, which are wont to defend themselves with the best arms given them by nature; bulls with their horns, horses with their hoofs, and cats with their claws; wherefore an old man should at least show himself to be as wise as the brutes, and maintain his position by his wisdom and knowledge, seeing that all the grace and power of his manhood must needs have fled.

Cardan's pessimism was founded on his own life experience, and for sheer intensity, has probably never been rivalled. In spite of wordly success Cardan was essentially an unhappy person, due in part to the obstacles he had to overcome because of his illegitimate birth, and in part to the execution of his only son for murder. His personal sufferings did not prevent his mind from ranging, in true Renaissance fashion, over broad fields of activity. In addition to medicine, physics, mathematics and philosophy, he made practical suggestions of value for the education of the blind and deaf. His attitude toward the advanced years is summed up in this terse sentence: "Old age, when it comes, must make every man regret that he did not die in infancy."

At this time we leave the medical authorities and turn to two distinguished lay writers, Cornaro, the Italian (1467 or 1475-1566) and Montaigne, the Frenchman (1533-1592). Both had wide influence in their own and succeeding centuries. Both are well worth reading today, since in each we find originality of thought, action and expression, and unusual freedom from outworn scholasticism.

Although all the classical and medieval writers on old age had highly recommended sobriety and temperance, Cornaro developed an extreme regimen which he followed faithfully from about the age of forty until his death. He tells us how overindulgence in food and drink, as well as a strong propensity to anger and emotional outbursts had so upset his health that he was continually racked by pain and other bodily distresses. Wherefore he resolved to limit himself to twelve ounces of solid food, and fourteen ounces of liquids. In addition he determined to avoid heat, cold, fatigue, grief and other emotional strain. In order to carry out these resolves a highly secluded life would seem obligatory,



FIG. 3. Cornaro and His Family.. An engraving after a painting by Titian

but such does not appear to have been the case. The ascetic way of life first planned at forty years, found Cornaro at an advanced age so robust and sturdy that he felt impelled to tell his contemporaries about his successful methods. This first essay, written at 83, was entitled, *A Treatise on a Sober Life*, and was followed, according to the customary dating, by three others, at the ages of 86, 91 and 95 years.

Readers of Thoms' work on *Human Longevity, Its Facts and Fictions* (8) will not be surprised to learn that the customary dates ascribed to Cornaro's life and writings require revision in the light of modern research. Professor Sarton (9) quotes Giordano to the effect that the usual ages given for Cornaro's

discourses, 83, 86, 91 and 95 years, are based on the assumption that he was born in 1467, but that Rossi now considers most probable that Cornaro was born in 1475 and died on May 8, 1566. On that basis Cornaro's discourses were composed at the ages of 75, 78, 83 and 87. This new viewpoint revises Cornaro's age downward by eight years, and somewhat dims his absolute achievement in attaining long life through following his own prescriptions. On the other hand, it in no way detracts from the charm or value of Cornaro's work nor from its widespread influence. It was early translated into French and English, was recommended at length by Addison in the *Spectator*, October 13, 1711, and was reprinted as recently as 1912 by Butler, (Milwaukee) in an illustrated and annotated edition (10). Two paintings of Cornaro are extant, a portrait by Tintoretto in the Uffizzi Gallery in Florence, and an engraving after Titian showing the patriarch surrounded by grandsons and their children (fig. 3).

Today Cornaro's methods have fresh significance for us in view of modern work in nutrition and becomes even more attractive in the light of McCay's work in promoting the longevity of his laboratory rats through systematic undernutrition. Cornaro's attitudes and ideas may best be understood from careful perusal of his little book, but a few quotations will serve to give some savor of this determined old Venetian.

*"Now, Nature does not deny us the power of living many years. Indeed, old age, as a matter of fact, is the time of life to be most coveted, as it is then that prudence is best exercised, and the fruits of all the other virtues are enjoyed with the least opposition; because, by that time, the passions are subdued, and man gives himself up wholly to reason."*

*The First Discourse.*

*"In this manner, I accustomed myself to the habit of never fully satisfying my appetite, either with eating or drinking—always leaving the table well able to take more. In this I acted according to the proverb: 'Not to satiate one's self with food is the science of health'."*

*Ibid.*

*"And now, since some sensual and unreasonable men pretend that long life is not a blessing or a thing to be desired, but that the existence of a man after he had passed the age of sixty-five cannot any longer be called a living life, but rather should be termed a dead one, I shall plainly show they are much mistaken; for I have an ardent desire that every man should strive to attain my age, in order that he may enjoy what I have found—and what others, too, will find—to be the most beautiful period of life."*

*Ibid.*

*"In conclusion, I wish to say that, since old age is—as, in truth, it is—filled and overflowing with so many graces and blessings, and since I am one of the number who enjoy them, I cannot fail—not wishing to be wanting in charity—to give testimony to the fact, and to fully certify to all men that my enjoyment is much greater than I can now express in writing. I declare that I have no other motive for writing but my hope that the knowledge of so*



*great a blessing as my old age has proved to be, will induce every human being to determine to adopt this praiseworthy orderly and temperate life, in favor of which I ceaselessly keep repeating, Live, live, that you may become better servants of God!*

*The Fourth Discourse.*

A contemporary reaction to Cornaro's work is to be found in Leonardus Lessius, a learned Jesuit of Louvaine, who according to Mackenzie, lived about the end of the sixteenth century, and was so much pleased by Cornaro that purely to recommend his efforts wrote a book entitled, *Hygiasticon, or the true method of preserving life and health to extreme old age*.

Michel Eyquem, Seigneur de Montaigne (1533-92) brings to the subject of old age the keen insight, sharp observation, kindly humor and realism that have kept his essays a part of the living literature of all time. His tolerant spirit and easy style give no room to false optimism, and nowhere does the writer allow himself any illusions about the discomforts of growing old. His attitude is summed up thus: "... old age stands a little in need of a more gentle treatment. Let us recommend it to God, the protector of health and wisdom, but withal, let us be gay and sociable." Compared with Cardan, who found nothing worthwhile in advancing years, Montaigne is still able to poke fun at himself, at physicians, and at those who put too much faith in physicians.

In attempting to choose extracts from the *Essays*, that may give the reader insight into Montaigne's spirit, the wealth of material worthy of quotation makes decision difficult. This work (11) and that of Cornaro, are required reading for both doctor and patient interested in old age.

*"But nature, leading us by the hand, an easie, and, as it were, an insensible pace, step by step conducts us to that miserable condition, and by that means makes it familiar to us, so that we perceive not, nor are sensible of the stroak then, when our youth dies in us, though it be really a harder death than the final dissolution of a languishing body, which is only the death of old age."*

*"No old age can be so ruinous and offensive in a man who has past his life in honour, but it must be venerable, especially to his children; the soule of which he must have train'd up to their duty by reason, not by necessity, and the need they have of him, not by roughness and force."*

*"Our wits grow costive and thick in growing old."*

*"Let us a little permit nature to take her own way; she better understands her own affairs than we. But such a one died, and so shall you, if not of that disease, of another. And how many have not escap'd dying who have their physicians always at their tails?"*

*"The gout, the stone, and indigestion are symptoms of long years, as heat, rains, and winds are of long voyages."*

*"Sometimes the body first submits to age, sometimes the soul, and I have seen enow who have got a weakness in their brains before either in their hams, or stomach; and by how much the more, it is a disease of no great pain in the infected party, and of obscure symptoms, so much greater the danger is."*

This review of the leading opinions regarding old age in the sixteenth century may be concluded with the work of Montaigne's countryman, Andre du Laurens, or Laurentius (1558-1609). This eminent practitioner, a physician to Marie de Medici and Henry IV, was not a great originator, and while no important discoveries are attributed to him, his writings achieved importance in his own day. In his *Opera Anatomica*, Lyon, 1593, he defended Galen against his detractors, Vesalius and Columbus, and yet he was far from being blindly bound by outworn authorities. This is well shown in his work on old age, published



FIG. 4. André du Laurens (1558-1609). (From print in the collection of The Home for Aged and Infirm Hebrews, N. Y.).

in French at Paris in 1597. There were nine French editions, two Italian and several Latin translations. The English translation by Richard Surphlet appeared in 1599, and is entitled, *Discourse of the Preservation of the Sight; of Melancholike Diseases; of Rheumes, and of Old Age* (12).

Laurentius was a thorough Galenist in his interpretation of aging, considering it as a result of the moisture of the body being consumed by its heat, and producing the characteristic coldness and dryness seen in the old. Nevertheless he was wise enough to make first hand observations bearing on certain questions which continued in dispute for centuries. "The Men of Egypt and Alexandria did believe that the naturall cause of olde age did come of the diminishing of the

heart; they said that the heart did grow till fiftie yeares the weight of two drames every yeer, and that after fifty yeeres it waxed lesser and lesser, till in the end it was grown to nothing; but these are nothing but vaine imaginations and fooleness. We have caused many old men to be opened, whose hearts have been found as great, and heavie as them of younger sort." This question continued to perplex physicians until relatively recently, and the wide discrepancies in weight of the heart were not clarified until the rôle of hypertension in causing cardiac hypertrophy was appreciated.

In general all ancient writers on old age are concerned with it as an entity, as expressed in the epigram attributed to Terence, *Senectus ipsa est morbus*. Laurentius differentiates a natural old age, corresponding to what we call aging in the biological sense, and a pathological old age, *Senium ex morbo*. He defines external as well as internal causes of aging, the inevitability of which he emphasizes again and again, pointing out the worthlessness of the time honored quack remedies. "All the precious licours that are, Aurum potabile, conserves of Rubies and Emeralds, Elixir vitae, or the faimed and fabulous fountain of restored youth cannot withstand, but that our heate must at length grow weake and feeble."

"... I leave to speake of all other outward causes, (as over violent exercises, and idle and sitting life, long and continuall watching, the passions of the minde which of themselves can make us olde, as feare and sadness), because we may in some sort avoide and shun them. I leave also to say anything of chancing causes, or such as may befall us by haphazard as hurts: I am only purposed to shoew that it is of necessitie that every living creature must waxe olde, that he fostereth within himself the naturall causes of his death, and that he hath outward causes thereof hanging about him, which cannot be avoided."

Laurentius understands the significance of the mind, the importance of diet, of alcohol and of occupation for the aged. He points out too, that different men age at different rates of speed, some being old at forty and others young at sixty, attributing this to their bodily make-up. "They which are of a sanguine complexion, grow old very slowly, because they have a great store of heate and moysture; melancholike men which are cold and drie, become old in shorter time."

The views of this distinguished French physician may be taken to summarize the best thought of his day on old age and they represent the advance of learning to the point just antecedent to the great and sustained progress of medical science which followed upon Harvey's revolutionary discovery and the application of the microscope to anatomical study by Malpighi, which in turn led to the correlation of clinical and post-mortem findings by Morgagni. It is interesting to look ahead and see in the course of the years how many different causes have been assigned to aging, with the result that today we believe it to be a biological process, an inherent property of the germ plasm. *Senectus ipsa est morbus* may have re-established its right to serious consideration as a principle, but actually our modern interpretation is at the same time both broader and more restricted than the old time philosophers conceived it; broader in the sense that we think

of aging as a fundamental property of living, and perhaps also of inanimate matter; more restricted in that we are gradually becoming more and more precise in the differentiation of true aging from the superimposed disease-processes.

## REFERENCES

- (1) WAITE, A. E.: The Hermetic and Alchemical Writings of Paracelsus the Great, London, Elliott, 1894. Quotations taken from, A Book Concerning Long Life, Vol. 2, p. 330.
- (2) LOB DER HEILKUNST; aus dem lateinischen uebertragen und erlaeutert von Ludwig Enthoven, Strassburg, J. H. E. Heitz, 1907, vol. 7, p. 8.  
The very rare English translation,—one copy in the Osler Library at McGill University, Montreal, Canada; the other in the Huntington Library, San Marino, Calif., —is entitled *Declamatio in laudem artis medicinae. A declamacion in the prayse of physyke, newly translated*, 8, R. Redman. No author, date or place is given.
- (3) ZERBI, G.: Ad Innocentam VIII, Pon. Max. Gerontocomia feliciter incipit. Prologus. Rome, 1489.
- (4) ZEMAN, F. D.: The Gerontocomia of Gabriele Zerbi, A Fifteenth Century Manual of Hygiene for the Aged, J. Mt. Sinai Hosp., 8: 5, 1161, 1942.
- (5) Only two copies of this odd little book are known, one in an English library, the other in the Huntington Library, San Marino, Calif., through whose courtesy the writer was privileged to read the book in microfilm. It is mentioned by S. V. Larkey in his excellent introduction to the Shakespeare Association's edition of Surphlet's translation of Laurentius' Discourse of Preservation of Sight.
- (6) (1) De Senectute, J. Cardan, in his Opera, Lugdini 1663, VI, 242-298. (See Index Cat. S. G. L., vol. i.) (2) Hieronymus Cardanus, Opuscula medica senilia in quattier libros tributa, quorum i; De Dentitus, ii; De Rationali Curandiratione, iii; De facultatibus medicamentorum, praecipue purgatum, iv; De morto regio. Bunia nunc primum ex Ms. Bibliotheca romanam lucem data. Lugdini: Sumpt. L. Durand, 1638, p. 531.
- (7) WATERS, W. G., CARDAN, J.: A Bibliographical Study. London, Lawrence and Bullen, Ltd., 1898.
- (8) THOMS, W. J.: Human Longevity: Its Facts and Fictions, London, J. Murray, 1873.
- (9) SARTON, G., HOEFER-AND CHEVREUL, with an excursus on creative centenarians. Bull. Hist. Med., 8: 441.
- (10) CORNARO, L.: The Art of Living Long. A New and Improved English Version, Milwaukee, Wm. F. Butler, 1915.
- (11) The Essays of Michael, Seigneur de Montaigne, ed. 3, London, 1700, made English by Charles Cotton, London, Alex. Murray & Son, 1870. Reader is referred also to the Life of Montaigne, compiled from the Essays by Marvin Lowenthal, New York, Houghton Mifflin Co., 1935.
- (12) See Shakespeare Association Facsimiles No. 15, published for the Shakespeare Association by H. Milford, London, Oxford Univ. Press, 1938, for reprint of Surphlet's Translation of Laurentius, with an excellent introduction by Sanford V. Larkey, to whom the present writer is indebted for his information on this author.

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Isodose Charts for Fields of Special Usefulness in the Treatment of Cancer of the Uterine Cervix.* S. M. SILVERSTONE. *Am. J. Roentgenol.*, 49: 6, June, 1943.

With the limiting diaphragm the author finds that the beam is uniform and that there is no penumbra. A roentgenogram reveals an homogeneous shadow sharply defined for the specified field size. The maximum doses on the surface and in the depths of a phantom are obtained. The result is a more uniform distribution of doses of an irradiated field. The output for any target surface tension is independent of the size of the field and is slightly greater than if a limiting diaphragm were used.

*A Rapid Test for Tumor Growth Inhibitors.* D. LASZLO AND C. LEUCHTENBERGER. *Cancer Research*, 3: 401, June, 1943.

The determination of the inhibition of tumor growth is established by comparing tumor sizes and tumor weights of treated groups with untreated controls at the end of an experimental period of 48 hours. The growth rate of sarcoma 180 is used as the indicator. Seven to ten days after transplantation batches of at least 7 mice each with comparable tumor size are selected. One group is injected twice daily intravenously for two consecutive days with the material to be tested, another with a standard of reference, and a third with saline for control. Forty-eight hours later, the tumor sizes and tumor weights are determined. The technique and the conditions for the standardization are described in detail and the material is analyzed statistically. The practical application of this rapid test for the detection of tumor growth inhibitors in various sources, such as brewer's yeast, grains, pure chemicals and the use of this test for tracing inhibitory activity of chemical fractions are demonstrated.

*The Tocopherol Level in Human Serum During Oral Tocopherol Therapy.* I. S. WECHSLER, G. G. MAYER, AND H. SOBOTKA. *Proc. Soc. Exper. Biol. & Med.*, 53: 170, June, 1943.

In continuation of previous studies, the tocopherol level in the serum of patients with amyotrophic lateral sclerosis and with miscellaneous myopathies was found to average 0.67 and 0.61 mg./100 ml. respectively. The response to daily oral administration of 75 to 740 mg. tocopherol runs parallel to the dosage and attains levels of more than 2.0 mg./100 ml. serum. Temporary favorable effects on the clinical status are only found with doses over 200 mg. tocopherol per diem. The spinal fluid does not contain tocopherol.

*Newer Concepts in the Diagnosis of Congenital Heart Disease.* M. L. SUSSMAN. *Am. J. Dis. Child.*, 65: 922, June, 1943.

The common congenital lesions of the heart are discussed in the light of appearance of cyanosis, physical signs, circulatory dynamics, electrocardiographic and angiocardiographic findings. Careful application of the principles discussed usually permits precise diagnosis of the predominant lesions. Occasional cases present themselves which defy exact analysis. Fortunately however, the lesion which has been found to be amenable to surgical cure, patent ductus arteriosus, can now be diagnosed with certainty in most cases.

*The Roentgenologic Diagnosis of Right-Sided Enlargement of the Heart.* M. L. SUSSMAN. *New England J. Med.*, 228: 777, June, 1943.



The roentgenologic configuration of the heart in various diseases associated with right-sided enlargement has been analyzed with the aid of angiocardiology. It was found that considerable enlargement of the right ventricle can occur without any demonstrable change in the size or shape of the heart unless serial roentgenograms are available. Widening at the apex with convexity of the interventricular septum to the left instead of to the right found by angiocardiology cannot be seen in the conventional roentgenologic examination. With increasing dilatation of the right ventricle the transverse diameter increases to the left. Finally, especially when right auricular dilatation takes place, there is cardiac enlargement to the right and anteriorly as well as elevation of the right cardiac-supracardiac junction.

Right-sided enlargement of the heart is often associated with dilatation of the pulmonary artery. Hence, in certain diseases, prominence of the middle left cardiac segment is an indirect indication of right ventricular dilatation.

In mitral disease the large left auricle displaces the right ventricle anteriorly and to the right. The pulmonary artery is elongated and elevated anteriorly and cephalad. The convex or straightened middle left segment of the cardiac contour is due primarily to the large left auricle. The degree of right-sided enlargement in this condition may be difficult to evaluate.

*Dermatitis from Resin Glues in War Industries.* L. SHWARTZ, S. M. PECK, AND J. E. DUNN. Public Health Reports, 58: 899, June, 1943.

Dermatitis from synthetic resins used in industries are described. The composition of the glues are given. Phenol formaldehyde and urea formaldehyde resins are the most frequent causes of dermatitis from the resin glues. The synthetic resins are both primary irritants and sensitizers. It is the unpolymerized resins which cause dermatitis. Completely polymerized and cured resins usually do not lead to dermatologic manifestations. Prevention of dermatitis from these substances among the workers using them is discussed in detail.

*Isodose Charts for Fields of Special Usefulness in the Treatment of Cancer of the Uterine Cervix.* S. M. SILVERSTONE, C. B. BRAESTRUP, AND B. S. WOLF. Am. J. Roentgenol., 49: 819, June, 1943.

Radiotherapy of carcinoma of the cervix which is more extensive than Stage 1 is made difficult by the necessity of securing a cancericidal dose throughout the true pelvis without causing incapacitating damage to the normal tissues—specifically, the bladder, the intestines, and the femoral neck.

In the ordinary case of cervical carcinoma, the dosage obtained from intrauterine and intravaginal radium is cancericidal to within 2.5–3.0 cm. from the endocervix. Within this volume, it is unnecessary and may be dangerous to add external radiation. Therefore, a special field is suggested for external radiation consisting of a square 15 x 15 cm. with a central lead strip 4 cm. wide. Actually this arrangement is equivalent to two fields separated by 4 cm. but treated simultaneously in a technically simple setup. The depth dose curves for such a split field had to be investigated in order to determine the distribution of dose underneath the central lead strip, i.e., the dose that the bladder, cervix and rectum would receive. It was found to be 20 per cent or less of the skin dose and thus minimized damage to the surrounding normal structures.

In addition, the depth dose curves for a 10 x 15 cm. field were measured with special attention to the dose at and beyond the periphery of the beam. It was found that, contrary to many previously published isodose curves, the margin of the beam was quite sharp, i.e., showed a steep fall in dosage. This sharpness of the field however, was obtained only after redesigning the collimation of the cones. Such redesigned cones make possible "sharp-shooting," so that the femoral head and neck can be excluded from the direct beam. This is of great advantage in preventing injury to normal tissue.

*Treatment of Spontaneous Breast Cancers in Mice with Pearled Barley.* R. LEWISOHN, C. LEUCHTENBERGER, R. LEUCHTENBERGER, D. LASZLO AND Z. DISCHE. *Proc. Soc. Exper. Biol. & Med.*, 52: 272, April, 1943.

The authors presented in previous papers their results with intravenous injections of yeast extract in the treatment of spontaneous breast adenocarcinomas in mice. They reported complete disappearance of these cancers in 30 per cent of the animals, if the tumors were not of excessive size. In their last publication they reported that by combining the injections of yeast extract with a diet of polished rice they were able to double the percentage of complete regressions and to get these results not only in small tumors, but in tumors of considerable size.

In this preliminary report they present results obtained by treating mice with intravenous injections of polished barley extract and a diet of polished barley or polished rice. Before the treatment is started the diagnosis of malignancy is made definite by a biopsy. During the course of the treatment the animals lose between 2 and 10 gms. However, the beneficial effect of this diet on tumor growth cannot be ascribed to a deficiency in the diet. Evidently this diet contains substances which counteract and inhibit tumor growth. Results in control animals are presented.

The changes which occur in these tumors following this combined treatment are most remarkable. After a few treatments hemorrhagic tumors show a whitish color. Hard tumors change to a soft consistency. In many cases the whole tumor is expelled, leaving a flat cavity which heals completely after a few days. In a set of 46 animals, 19 mice showed complete disappearance of their spontaneous breast adenocarcinomas.

*Vitamin A Studies in Cases of Ichthyosis.* S. M. PECK, A. W. GLICK AND L. CHARGIN. *Arch. Dermat. & Syph.*, 48: 32, July, 1943.

Vitamin A studies were made in 2 cases of congenital ichthyosis. The levels of vitamin A in the blood were decidedly below normal. Studies of dark adaptation showed a cone threshold at the upper limit of normal in case 1 and a rod and cone threshold well above normal in case 2. These observations apparently indicate a relation between vitamin A metabolism and the condition of the skin in such cases. Large doses of vitamin A, whether given orally or intramuscularly, easily restore the level of vitamin A in the blood to normal. Even if such a normal level is maintained for a long time, there is little, or no, effect on the clinical course of the disease.

*Von Recklinghausen's Neurofibromatosis.* B. W. BILLOW. *Am. J. Surg.*, 61: 1, 128, July, 1943.

Multiple neurofibromatosis is a constitutional and hereditary disease with protean manifestations. It is much more common than supposed. The author's figure based on a survey of five-hundred people during a month's period reveal it present among 1.6 per cent of the population. Its chief features and most common signs are soft elastic pinkish nodules along the course of peripheral nerves, known as molluscum fibrosum, a pigmented café-au-lait colored patches, scoliosis, endocrine dyscrasis, mental changes and defects in hearing and sight. A case is reported associated with a hepatomegaly and splenomegaly along with the common skin manifestations.

*The Influence of Electric Current Application on the Structure of the Brain Of Dogs.* J. H. GLOBUS, A. VAN HARREVELD, AND C. A. G. WIERSMA. *J. Neuropath. & Exper. Neurol.*, 2: 263, July, 1943.

A careful gross and microscopic study of brains of dogs subjected to electronarcosis disclosed no pathologic alterations. The brains of the experimental animals did not differ anatomically from that of the normal control. There were no changes in the size, the consistency, and the vascularization of the brain tissue, nor were there any alterations in the nature or number of the nerve cells. There were no changes in the glial elements, nor in the structure, content and the environment of the blood vessels, and no abnormal accumulation

of pigment or of fatty products of dissolution were found. It is significant that the histologic structure of the brain in the animal killed by electrocution did not differ from that in the other experimental and control animals.

*Vitamin A Studies in Cases of Keratosis Follicularis (Darier's Disease).* S. M. PECK, A. W. GLICK, H. H. SOBOTKA AND L. CHARGIN. Arch. Dermat. & Syph., 48: 17, July, 1943. Ten cases of keratosis follicularis (Darier's disease) have been studied.

In 8 of the cases the vitamin A content of the blood serum was below normal levels, and in 2 cases it was at the lower limits of normal. The carotene content of the blood was within normal limits.

In the 5 cases in which studies of dark adaptation were made, good correlation was obtained between the threshold for dark adaptation and the vitamin A deficiency as evidenced by the vitamin A content of the serum. The threshold for dark adaptation was higher than normal before vitamin A therapy was instituted.

In 9 of the cases there was gradual improvement of the cutaneous lesions with oral administration of approximately 200,000 U.S.P. units of vitamin A daily. This was preceded by a restoration of the vitamin A content of the blood serum to normal. When vitamin A therapy was discontinued, there were a gradual return of the cutaneous manifestations of this disease and a decrease in the vitamin A of the blood to the former low level, even when the diet contained adequate amounts of vitamin A for the normal person.

The first histologic evidence of improvement was the decrease in the epidermal edema, a striking pathologic feature. The last pathologic change to disappear was the dyskeratosis i.e., the corps ronds.

Keratosis follicularis (Darier's disease) is a disease of vitamin A deficiency. There seems to be either a hereditary or an acquired weakness in absorption of vitamin A or in conversion of provitamin A to vitamin A which reflects itself in the skin as a dyskeratosis.

*Pentosuria Associated with Diabetes Mellitus.* M. H. EDELMAN AND M. REINER. Arch. Int. Med., 72: 31, July, 1943.

The histories and findings in two cases of essential pentosuria are presented. The co-existence of diabetes mellitus with essential pentosuria was discovered in one of the obese cases and it is emphasized that they are two distinct entities and bear no relation to each other.

The criteria for the diagnosis of essential pentosuria are as follows: (1) the continuous excretion of small amounts of pentose in the urine unrelated to diet (2) the absence of symptoms (3) history of hereditary pentosuria when obtainable and (4) a normal dextrose tolerance curve unless there is associated diabetes mellitus.

Tests for the identification of pentose are tabulated and discussed. The clinical importance of recognizing essential pentosuria is stressed.

*Cold Agglutinated Erythrocytes: Hemolytic Effect of Shaking.* D. Stats. Proc. Soc. Exper. Biol. & Med., 54: 305, August, 1943.

Concentrated erythrocyte suspensions subjected to marked cold agglutination are readily hemolyzed by shaking. The amount of shaking is not sufficient to hemolyze relatively weakly agglutinated or non-agglutinated erythrocytes. Light erythrocyte suspensions are not hemolyzed. Hemolysis occurs in the absence of complement and only at low temperatures. Hemolysis of cold agglutinated erythrocytes is different from the hemolysis of the Donath-Landsteiner phenomenon. In the latter hemagglutination is slight; erythrocytes sensitized in the cold by amboceptor are hemolyzed at 37°C. by complement, hemolysis failing to occur in the cold.

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## THE EDWARD GAMALIEL JANEWAY LECTURES

## ASPECTS OF THE TRANSMISSION OF THE NERVOUS IMPULSE

## II. THEORETICAL AND CLINICAL IMPLICATIONS

OTTO LOEWI, M.D., Sc.D. (Hon.)<sup>1</sup>

In the first lecture I discussed the occurrence and the extent of the chemical transmission at peripheral and central synapses. In today's lecture I want to start dealing with the intimate mechanism of the transmitter function. Considering first the site where the transmitters are released we can obviously make the statement that this is the synapse, since the transmission takes place from the nerve endings to the effector organs. A synapse is not an anatomical conception. It is a purely functional one, meaning the place where the nerve ending makes contact with the cell. Liberation of the transmitter at the synapse naturally means its liberation from the nerve endings; otherwise it could not be the transmitter of the nervous impulse to the effector organ. That it really is liberated from the nerve endings was to be anticipated. There is also direct and conclusive evidence of the correctness of this assumption. It can for instance be shown that after degeneration of the preganglionic sympathetic fibres the superior cervical ganglion loses its whole Ac.Ch. content. Since the ganglion itself does not degenerate, the Ac.Ch. must have been derived from the endings of the preganglionic nerve fibers located within the ganglion.

Here arises the question of the mode of the liberation of the chemical transmitters. In the resting state of the nerve the transmitters cannot be present there in a free diffusible form but they must be in a non-diffusible combination. This becomes evident by the mere fact that Ac.Ch. is to be found within the nerves. If Ac.Ch. were diffusible, it would be destroyed by the esterase which is present everywhere. This is not an assumption only for I could prove it by showing that the acetylcholine content of intact organs remains constant for hours. But Ac.Ch. that is added to the organs is quickly destroyed (1).

Another proof is the fact that practically no Ac.Ch. or adrenaline diffuses into the circulating fluid of organs without nervous stimulation. If the transmitter were diffusible, the heart, for instance, would be continuously intoxicated since 1/500th part of the amount of transmitter constantly present in it is sufficient to produce a maximal effect. We have, therefore, to conclude that Ac.Ch. or adrenaline as the case may be is present in the intact organ in some labile non-diffusible combination in which it is inactive and not subjected to attack by esterase. By the way several scientists have succeeded in demonstrating the presence of such combinations of Ac.Ch. in nervous tissue which they call Ac.Ch.-precursors. Consequently, we have to assume that the nervous impulse acts in

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such a way that it liberates the transmitters from their indiffusible combination present in the nerve terminals and that the liberated, free transmitters diffuse from there to the effector organs.

What is the origin of the Ac.Ch. present in the nerves and by what mechanism is its loss, caused by nervous stimulation, replaced?

There exists no doubt that the nerves themselves are able to synthesize Ac.Ch. The fairly large amount present in most of the nerves cannot have been transported there from elsewhere by the blood since this contains so much esterase that not a minute trace of Ac.Ch. has been detected there. In addition within the last few years direct experimental evidence has been given for the occurrence of Ac.Ch. synthesis by nervous tissue. Quastel (2) was the first to show that minced brain tissue synthesizes Ac.Ch. under the condition that oxygen and glucose or pyruvate are present and Nachmansohn (3) reported the presence in homogenized nervous tissue of an enzyme called by him cholinacetylase which synthesizes Ac.Ch. in the presence of fluoride, eserine and choline in absence of oxygen and glucose under the condition that adenosinetriphosphate as source of free energy is present. The occurrence of Ac.Ch. synthesis directly in nerve terminals was also proven. Macintosh (4) perfused the superior cervical ganglion with eserinated oxygenated Ringer solution containing no glucose and continuously stimulated the preganglionic fibres. The Ac.Ch. content of the ganglion and of the perfusion fluid and consequently the effect of nervous stimulation was quickly decreased to a minimum. Continuation, however, of the stimulation after the addition of glucose or pyruvate to the perfusion fluid almost immediately increased the release of Ac.Ch. and restored the effectiveness of stimulation.

The question that naturally arises at this point is: through what kind of a mechanism does the nervous stimulation liberate the chemical transmitter? When an impulse is carried down a nerve electrical studies of the nerve at any point indicate the passage of a wave of electrical potential changes, known as the action potential. This action potential is presumed to manifest itself as a result of a change in the normal ionic permeability-relationships between the nerve and its environment. Hereby salts can move across the nerve membrane. This results in a change of the ionic concentration inside and outside whereby an electrical potential is produced. It has been assumed for a long time that especially potassium salts are involved in this movement. As a matter of fact Cowan (5) in 1934 in experiments later on confirmed by Young (6) in Fenn's Laboratory was able to show by direct chemical determinations that stimulation of a nerve caused leakage of potassium out of the nerve. This liberation of potassium could in its turn cause the release of transmitters from the nerve endings for the following reason: we know about quite a few cases which prove that potassium injected in relatively small amounts provokes the release of Ac.Ch. from nerve endings. Brown and Feldberg (7), for instance, have shown that addition of small amounts of potassium to the perfusion fluid of the superior cervical ganglion provokes a release of Ac.Ch. from the ganglion and its diffusion into the perfusion fluid exactly like preganglionic stimulation. Furthermore, Feldberg and Guimaraes (8) were able to show that injection of potassium liberates Ac.Ch. in the

tongue and in the salivary glands like stimulation of the chords. The amount of liberated Ac.Ch. is increased by previous eserization. Finally, as Feng (9) has shown, the facilitation in the striated muscle produced by intra-arterial injection of potassium is also increased by eserization exactly like that produced by previous tetanization.

All these cases demonstrate that potassium releases Ac.Ch. from the nerve endings and since nerve stimulation liberates potassium within the nerve, I feel entitled to assume that by this mechanism nervous stimulation causes the release of Ac.Ch. from the nerve terminals.

So far we have dealt only with the question of synaptic transmission. For this the presence of transmitters exclusively in the nerve terminals is needed. A great many observers, however, found Ac.Ch. also within the nerve stems. This fact suggested first to Italian scientists Calabro (10), later on Bergami (11) the idea that Ac.Ch. might play a part also in the transmission, that means in the propagation of impulses within the nerve stem itself. As a matter of fact they found, and this result later on was repeatedly confirmed, that if the ends of cut nerves are dipped in Ringer solution during artificial or natural stimulation of the nerves Ac.Ch. is released into the Ringer solution. In 1937 von Muralt (12) starting from the same idea published a paper in which he claimed to have shown that in the nerve stimulated under appropriate conditions more of an Ac.Ch.-like substance was present than in the non-stimulated paired nerve. A further approach to this question started from observations made on electrical fishes. In confirmation of an old finding of Garten (13), Auger and Fessard (14) in 1938 found that the electrical organ after degeneration of its nerves is not electrically excitable. This suggested to these investigators the possibility that the normal discharge by nerve stimulation might not be caused electrically but by the release of a polarizing or depolarizing substance from the nerve terminals. The electrical organs are looked upon as modified motor endplates in which later Marnay and Nachmansohn (15) had found a high concentration of cholinesterase. This suggested to Nachmansohn the possibility of a similar mechanism of nervous action at both structures the more, since already in 1937 Marnay and Nachmansohn (16) had found in the electrical organ too a cholinesterase concentration of similar order of magnitude as in the motor endplates of the muscle.

In fact in 1939 Feldberg, Fessard and Nachmansohn (17) found that stimulation of the nerves of the electrical organ releases from their endings Ac.Ch. which by its depolarizing action causes the electrical discharge of the organ. It was to be expected that there existed a quantitative relation between the electromotive force of the discharge different in different species of fishes and between the concentration of cholinesterase needed for the destruction of the Ac.Ch. released. Nachmansohn (18) in fact found a close parallelism. Hence he drew the conclusion that Ac.Ch. metabolism and bio-electric phenomena are intrinsically connected. Since the latter are supposed to be surface phenomena, he investigated whether also in nerve stems Ac.Ch. metabolism is located at the surface. He really found that in the giant nerve of the squid, where the endoplasm can be separated from the sheath, the activity of almost the whole cholinesterase (19)

and in addition also that of those enzymes which are supposed to be needed for Ac.Ch. synthesis occurs in the sheath (20). Hence he has brought forward the hypothesis that Ac.Ch. is involved in the propagated impulse of the nerves in such a way that Ac.Ch. is liberated at the spot of stimulation and acts upon the membrane. The electrical potential may be produced directly by this action or indirectly. The indirect action would mean that Ac.Ch. would decrease the resistance of the membrane surface and that hereby a difference in ionic concentration inside and outside the membrane might be created which in its turn is responsible for the electrical potential. Since this is propagated as a wave one would obviously have to assume that the Ac.Ch., released at the spot of the impulse immediately after its action on the membrane, has to be destroyed and then to be resynthesized.

It has to be emphasized that the mere presence of a substance in an organ obviously does not give information about its physiological significance. Ac.Ch. and esterase are not everywhere where they are found connected with nervous function. This becomes evident by the fact that they occur also in organisms and organs devoid of any innervation. On the other hand propagation of impulses occurs in every living cell and cell complex independent of whether or not they contain Ac.Ch. It is, therefore, tempting to assume that the mechanism of the propagation of impulses is in principle the same everywhere. Yet it could be that within the nerves due to a special differentiation it might be different. There exist, however, facts which apparently are not fully consistent with the view that within the nerve Ac.Ch. is necessarily involved in the propagation of impulses.

First, I may remind you that within the stems of sensory nerves no Ac.Ch. at all or only traces could be detected in contrast to efferent cholinergic nerves which contain considerable amounts of it. Furthermore, it has been shown in Cannon's laboratory that after degeneration of the preganglionic fibres not a trace of Ac.Ch. was present in the postganglionic sympathetic fibres. Yet the conduction of nervous impulses was intact. According to Feldberg (21) in degenerating nerves the loss of the ability to synthesize Ac.Ch. precedes the loss of conduction. Furthermore, Rosenblueth and co-workers showed that nerves during fatiguing stimulation or during Wallerian degeneration had normal conduction at a time when their Ac.Ch. content was much reduced (22). Against the cogency of at least some of these arguments one could perhaps object that the amount of Ac.Ch. present in nerves does not indicate the amount which is needed for the production of the electric phenomena which may be quite small. Finally I have to refer to experiments dealing with the question at hand recently published by Cantoni and myself (23). It is obvious that if Ac.Ch. plays the part in the propagation of the nerve impulse attributed to it by Nachmansohn it must immediately after its action on the membrane surface be destroyed and then be resynthesized. We started in our experiments from the idea that inhibition of the destruction must abolish the nervous conduction. In order to prevent the destruction we injected frogs with eserine in such an amount that after washing and incubating the nerves, procedures which in non-eserinized animals completely destroy the Ac.Ch. of the nerves, not a trace of Ac.Ch. was destroyed.



Yet the conduction in the eserized nerves during lifetime was unimpaired. Against the conclusiveness of this result one could perhaps raise the following objection: in order to determine the Ac.Ch. content of the nerves we had of course to grind them up. Thereby their structure is destroyed and eserine is allowed to diffuse to all elements of the nerves. One could therefore perhaps assume that within the intact nerve the injected eserine does not reach the spots where the cholinesterase is located and acts. We have no knowledge about these spots. From all the available literature we do know, however, that eserine does inhibit cholinesterase activity in intact tissues. It can, of course, not be excluded that just nerve fibres present an exception from this quite general rule. I, therefore, have to say and the same could be said in regard to at least some of the other experiments quoted against the hypothesis that Ac.Ch. is involved in nervous conduction: they do not necessarily invalidate it but they do not support it either. At any rate we have to wait for a clear cut demonstration whether or not the nerve impulse releases Ac.Ch. within the nerve stem and whether this Ac.Ch. is indispensable for the conduction of the nervous impulse.

I have spent such a long time on the question of whether or not Ac.Ch. is involved in the propagation of the nervous impulse because for many decades the problem of its mechanism has been considered one of the most intriguing ones in physiology.

Following the natural sequence of events we now proceed to discuss the exact point of action of the transmitters at the peripheral synapses. Formerly it was quite generally believed that substances like the transmitters as well as a great many other so-called vago and sympatheticomimetic substances were effective by attacking and stimulating the nerves. There were two reasons for this assumption. The first was based on the fact that these substances have the same effect as the excitation of the respective nerves. Now we know that just the reverse is true: nervous stimulation acts like the substances because its effect is produced by the substances. The second reason was the manifestation of the action of antagonistic substances. It has been well known that after the previous application of atropine or ergotoxine the effect of the excitation of the respective nerves is abolished. From this action the conclusion was drawn that these antagonistic substances paralyze the nerves and since they paralyze the effect of the substances too, one has drawn the conclusion that these substances stimulate the nerves. We have, however, been able to prove that atropine (24) and ergotamine (25) do not paralyze the respective nerves. The proof is that after the application of these antagonistic agents nervous excitation is still effective in liberating the transmitters; the same condition was later shown to hold for the other antagonists, nicotine (26) and curare (27). After their application stimulation of the respective nerves or ganglia still liberates the transmitters. This result would obviously be impossible if the antagonists paralyzed the nerves since the function of the nerves consists in liberating transmitters. Actually Ac.Ch. and adrenaline and the whole related group act directly on the effector organ and the antagonists counteract this effect. The transmitters therefore act also after complete degeneration of the nerves.

It is remarkable that a particular transmitter, when artificially applied, should



act just at the points where it is normally liberated by nervous impulses, that is to say that it is exactly there that the effector cells are specifically prepared for its action. This preparedness is apparently connected with the specific innervation: acetylcholine for instance acts on the auricle of the mammals and the toad, which are innervated by the vagus but not on the ventricle, which is not. That the development of the organ sensitivity for the transmitters is dependent on their innervation is furthermore shown by the fact that the embryonic heart is almost insensitive to the action of Ac.Ch. and other vagomimetic substances as long as it is not yet connected with the vagus. This sensitivity once reached outlasts a subsequent degeneration of the nerve.

What is the cause of this dependence? In order to explain the specific sensitivity of sympathetically innervated cells to adrenaline, Elliott (28) in his classical paper "On the action of Adrenaline" assumed the existence of a special structure within these cells which he named "myoneural junction." I would not enter into the discussion on this point if this nomenclature was not still in general use in this country. It seemed unlikely to Elliott that the cells themselves acted upon by adrenaline were of a structure different from that of the other cells not influenced by adrenaline. He, therefore, assumed that by the union of the sympathetic fibres with the effector cells a particular structure which he called myoneural junction was developed and which he claimed to be the point of attack of adrenaline. This structure he assumed was developed on the cellular side; this meant that its trophic center was located in the cellular nucleoplasm. He was obliged to make this assumption in explanation of the well known fact that after nerve degeneration adrenaline is still active. Accordingly the myoneural junction, the assumed point of attack of adrenaline, could not have degenerated.

Are we obliged or even allowed to accept such a structure, the existence of which was assumed only in order to explain the point of attack of adrenaline on sympathetically innervated effectors? At the time of Elliott's paper nothing was known about the fact now conclusively established that there does not exist a direct anatomical union of nerves with their effectors but that the nerve pathway is interrupted at the synapse and that the nerve acts by releasing synaptical transmitters, by this means bridging the interval. This fact by itself renders the assumption of a myoneural junction impossible. We, therefore, should eradicate this work once and for all. Adrenaline and Ac.Ch. act somewhere on the cell itself. But this obviously does not answer the question raised by Elliott as to why the effector cells supplied with the respective nerves are sensitive to the respective transmitters. We know on the whole very little indeed about the point of attack and about the intimate mechanism of the action of chemical agents. Apparently most of them act on the cell surface. To give you just two illustrations of this fact: potassium is contained within the cells in an amount 30 times greater than in its environment; yet if we raise the potassium content of the environment only fourfold, the heart stops. Or: methylenblue possesses an atropine-like action on the heart. If one saturates its cells with methylenblue to such an extent that they are deeply stained and then removes just the surrounding dye by washing, the atropine action ceases; it returns, however, at

the very moment when a trace of methylenblue is added again. In the case which we are interested in, namely Ac.Ch. and adrenaline, Clark (29) was able to show that their actions too are surface actions. In order to exert these the drugs obviously must make contact with the surface. The surfaces of different cells are quite different. This is not astonishing since also the chemical arrangement of the different cells is a different one. How can one explain, however, that Ac.Ch. and adrenaline respectively which in general act on the same cell do act only if this cell has been provided with the respective nerves? I have just stated that the surfaces of different cells are different. But also the structure of the surface of one and the same cell is not homogenous but is composed of different substances. Therefore it is understandable that drugs may not combine with the surface as a whole but only with specific parts of it called spots or patches or receptors. This is true for Ac.Ch. and adrenaline too since Clark has proven that not more than 1/6000th of the surface of the heart need be covered by Ac.Ch. to obtain the drug's activity. Accordingly in order to interpret the fact that Ac.Ch. is effective only in cells supplied with cholinergic fibres and adrenaline only in such ones supplied with adrenergic fibres we have to assume that by the innervation the surfaces of the respective cells have acquired a specific pattern by being supplied with specific receptors. The possibility, however, must also be borne in mind that all cells have receptors for transmitters but that for unknown reasons their reaction to the transmitters is lacking. The fact that drugs combine only with specific patches of the surface explains why many of them act in minute quantities. As to the character of the patches we know very little. It is quite possible that among them are enzymes located at the surface. The question naturally now presents itself how does it happen that the contact of the transmitter with specific surface receptors leads to their action on the function of the cells involved? It must be assumed that the receptors on the surface are links in a functional chain. The influence therefore exerted on specific receptors might lead to a change of the pattern and function of the whole surface. In what may this change consist? It has been shown in some cases that the change of surfaces involves a change of their polarized state. In the case of our transmitters it was shown by Bacq and Monnier (30) and by Monnier and Dubuisson (31) that the inhibitory action of adrenaline as well as that of Ac.Ch. is preceded by an increase of polarization and the augmentary action by a decrease of polarization. The change of polarization may be responsible for the change of the cellular function. In fact Monnier and Dubuisson succeeded by increasing the polarization in producing all the effects of vagus stimulation on the heart. As to the mechanism by which a change of the polarization may act I quote the general assumption that changes of polarization alter the permeability especially for ions thereby producing electrical potentials with their consequences.

It goes without saying that it is only in some cases that the contact of chemical agents with specific surface receptors may produce a change of the polarization of the surface and thereby a change of the function of the cells themselves. In other cases chemical agents may act on the surfaces in a different way. This may depend on the character of the agents and of the receptors acted upon.

Take for instance the case of insulin: because of its high molecular weight and its colloidal character it is supposed not to enter the cell but to act on the surface and because of the minute quantity needed for its action it is to be assumed that it acts on specific surface receptors. There is, however, no reason for assuming that insulin acts by changing the polarized state of the surface. We do not know anything about its receptors and how they may be acted upon. We only know that the ultimate result of insulin action consists in a change of carbohydrate metabolism obviously caused by preceding alterations of enzymatic processes. So far in spite of numerous efforts it has been impossible to demonstrate a direct influence of insulin on one of these processes in cell extracts presumably containing the enzymes. The influence so far is observed only as long as the structure of the cells acted upon is intact. It must start as we have learned from a surface action; only in this way apparently can the orderly orientated course of the enzyme actions be induced. I personally am convinced that this holds true also for the normal metabolism. You may feel that this last discussion exceeds just a little the object of this lecture. However, since for years I have wracked my brain about questions concerned with the mechanism of drug actions I could not resist the temptation to touch on this subject. I apologize for this offence against the plain architecture of the lecture.

So far we have dealt with the function of the nerves and the transmitters released from them only in regard to their influence on the specific functions of their effector organs. We have learned that after previous application of substances antagonizing the effect of the transmitters as atropine, ergotoxine, nicotine, curare, stimulation of the respective nerves becomes completely ineffective. It might be assumed, therefore, that the nerve has no other effect on the specific function of the organs than to release transmitters. The question, however, still remains open whether the nerve has perhaps some other influence on the effector organ apart from that on its specific function.

As a matter of fact we do know about an influence of nerves on a general property of their effector organs which we now have to discuss.

We have mentioned above that the responsiveness of organs to the action of the transmitters and related substances starts only from the moment when the nerves have been connected with the organs and exert their function, consisting in the release of the transmitters. We have mentioned furthermore that this responsiveness once established in the embryonic organs outlasts the degenerative removal in the adult of the respective nerves. This on first sight seems to be contradictory. In order to explain it we have to bear in mind that the state of embryonic organs is not likely to be the same as that of adult organs. Since we know that the action of transmitters and related drugs is dependent on the state of the organs, the different behaviour of embryonic and adult organs in regard to their reaction to drugs is not a matter of surprise. There exists, however, a phenomenon closely connected with the question of sensitivity dependent on nervous activity which needs a special discussion. After removal of the respective nerves the responsiveness of the adult organs to directly attacking chemical stimuli once established during embryonic life is not only maintained but even

exaggerated. There exists, as a matter of fact, a hypersensitivity to them. Cannon (32) puts it in this way: "When in a series of efferent neurons a unit is destroyed, an increased irritability to chemical agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated." He calls this "A law of denervation." The fact had been known for a long time but most of the quantitative experiments have been performed within the last 15 years in Cannon's laboratory on a great variety of structures. The increased reaction is produced not only as a consequence of degenerative section of postganglionic fibres, but also in the case of decentralization, this means the severing of preganglionic fibres leaving in this way the ganglion with its postganglionic fibres intact. After decentralization the increase of reaction is not as great as after the denervation; according to Hampel (33) it amounts in the average only to one half. The most likely assumption is that it is the decrease in the amount of transmitters released from the nerve endings after severing of the preganglionic as well as of the postganglionic nerves, which is responsible for the onset of the increased reaction. Accordingly, the difference in its degree after denervation or decentralization respectively may be interpreted in the following way: in the case of denervation the postganglionic terminals are degenerated, therefore the transmitters are no longer present. In the case of decentralization the transmitters remain and though central innervation is cut there are still chemical stimuli acting on the ganglion which in turn becomes hypersensitive by its decentralization with consequent degeneration of the preganglionic fibres. These stimuli are not sufficient to guarantee a full activity of the ganglion but they exert a limited one leading to a restricted release of transmitters. This is shown for instance by the fact that Horner's syndrome—consisting in myosis, enophthalmos, and narrowing of palpebral fissure—is much less manifest after decentralization than after degenerative denervation. The same features apply to the striated muscles. Here, too, decentralization produced by cutting off the respective anterior horn cells from all ingoing impulses, as well as denervation, produced by severing the respective spinal nerves, create hypersensitivity. But in this case too the denervated muscle is much more sensitive to Ac.Ch. than the decentralized. This is shown by the fact that only the denervated muscle fibrillates. As to the nature of the stimuli continuously acting upon the hypersensitive structures one has to assume that among these are transmitters reaching them from elsewhere, since they act on the hypersensitive structures in incredibly small amounts. As a matter of fact, according to Brown, Feldberg and Dale (34) only one thousandth of that acting on normally innervated structures is needed. I may recall, furthermore, that Bender (36) has shown that fright induces the contraction of the muscles innervated by the facial nerve after its denervation and degeneration. This contraction was intensified by previous injection of eserine. The contracting stimulus, therefore, must have been Ac.Ch. conveyed from an unknown place to the muscle.

We finally have to consider the question of the nature of the increased reaction of decentralized or denervated organs. This increased reaction does not only apply to the transmitters but in addition to all the substances which act also on



non-denervated organs. Hence, we can conclude that it is not caused, as frequently has been claimed, by an incidental decrease of the amount of the enzymes responsible for the destruction of the transmitters for this would allow a greater amount of them becoming available for action. It has frequently been assumed that denervation and decentralization increase the permeability of the cells concerned for chemical agents. But first: how could cells stand such a state and yet indefinitely remain intact, as, for instance, the smooth muscles do, and secondly: we have mentioned that the reaction to chemical agents of denervated cells can increase a thousand times. Who, however, would be willing to assume that the cell permeability could increase a thousand times? We, therefore, in my opinion, have to assume that the increased reaction to chemicals and to other influences of denervated or decentralized structures as well is the expression of a true hypersensitivity, the essence of which so far we do not understand.

I should like to add that the careful study of the phenomena of hypersensitivity has already led to at least one therapeutical consequence: the fact that the hypersensitivity to circulating transmitters and other substances is far greater in the case of denervation than in that of decentralization has suggested that in cases of Raynaud's disease one should not denervate the vessels but decentralize them. It seems that the therapeutical effect has been much better.

So far we have limited the discussion about the production of hypersensitivity as a consequence of denervation or decentralization to peripheral organs only. I wish to emphasize, however, that as Cannon (37) has shown for the first time, and his results were confirmed by Ward and Kennard (38) and quite recently by Stavraký (39), the same holds true for the C.N.S., in other words in the C.N.S. too the removal of efferent neurons results in an increased sensitivity to chemical agents, among these also Ac.Ch., in the isolated structures. To my knowledge we are not aware whether or not this hypersensitivity due to the loss of transmitters plays a part in an eventual recovery of the functions of the isolated structures of the C.N.S.

We have started the whole question concerning denervation and its consequences in order to investigate whether or not the nerves in addition to their action on the specific function of the organs have still another influence on them. We have learned that in the embryo the sensitivity of the organs to chemical stimuli depends on the activity of the nerves and that in the adult after denervation and decentralization the efferent organ becomes hypersensitive to chemical stimuli. It may well be that what we call hypersensitivity in fact represents the genuine sensitivity of the cells which, however, as long as these are connected with their nerves is kept down by this influence.

From a teleological point of view such a function of the nerves is understandable. What would happen if the slightest stimulus would have its own direct influence independent of the coordination of the functions? At any rate the discussion has disclosed that the nerve has two functions: first, to conduct impulses in order to initiate or to modify the specific function of organs and secondly, to control the sensitivity of organs in regard to directly attacking stimuli. In this second function too, at least in the periphery, the transmitters are involved.



thereby may account for the disturbance of the motor function. The question as to whether in addition an agent is circulating which inhibits the synthesis of Ac.Ch. has to be decided by future work. This much, however, seems to be already established, namely that the myasthenic disturbance is caused by a pathological metabolism. The same apparently holds true for other muscular disturbances. Think of the muscle dystrophy caused by vitamin E deficiency. Furthermore, I should like to mention in this connection the following: in the only case of myotonia congenita which I had the opportunity to examine I dialyzed serum obtained from a limb during its sustained contraction and suspended in it a rectus abdominis muscle of a frog; on stimulation its relaxation was delayed exactly as it is during the application of veratrine, which as is well known mimics the pattern of myotonic muscle contraction.

Within the last years in quite another region of the body a connection between Ac.Ch. was produced and a specific function is assumed to have been discovered leading to a therapeutic consequence.

It has been known that estrine produces hyperemia in the uterus and that this is prevented by atropine. This latter fact suggested to Reynolds (46) the idea that the hyperemia following estrine injection may be produced not by estrine directly but by Ac.Ch. liberated by estrine. He reported indeed to have found an increase of Ac.Ch. in the uterus after injection of estrine in rabbits. Starting from these observations of Reynolds, which by the way later on were not confirmed by Macintosh (47), Soskin (48) got the idea that Ac.Ch. as an hyperemia provoking agent might play an important part in menstruation of woman and that delayed menstruation might be due to decreased responsiveness of the uterine vessels to the hyperemic stimulus of Ac.Ch. With this in mind he attempted to overcome this assumed poor responsiveness to Ac.Ch. by increasing the amount of the vasodilator stimulant Ac.Ch. For this purpose he injected prostigmine which protects Ac.Ch. from being split and thereby makes more Ac.Ch. available for action. As a matter of fact he succeeded in producing by prostigmine bleeding in all cases of delayed menstruation except in those which were due to pregnancy or to endocrine disturbances. Prostigmine, therefore, might perhaps be used as a therapeutic and at the same time as a pregnancy test. (There exist already quite a few but no yet sufficient reports which by and large seem to confirm Soskins's experiences.) Whether or not this may prove in the future to be of clinical value the discovery that prostigmine is able to produce bleeding is at any rate important from the theoretical point since it shows that Ac.Ch. present in the uterus plays a part as a hyperemia producing agent in menstruation. Future experiments are needed to find out whether, and incidentally by which mechanism, eserine produces or releases Ac.Ch. or influences its action in the uterus.

So much, or better, so little about the clinical consequences of the discovery of the chemical transmission.

Finally, I may be allowed to say a word concerning the question as to how the neuro-chemical mechanism fits into the other relations existing between the cells in the organs.

A characteristic of all living substance is its ability to react to stimuli. The

more we progress in our knowledge of the nature of stimuli the more the evidence increases that stimuli of chemical nature are predominant. Who would have thought for instance a few years ago that mechanical stimuli may act indirectly by producing effective chemical agents? And now we have learned that the nervous system exerts its effects by liberating chemical substances, effects, so far looked upon as being due to stimuli of quite another nature.

Is this really a matter of surprise?

Within the organismic cell complexes which lack nervous elements, the mutual relations of the cells obviously can be of no other than of chemical nature. Within the organismic cell complexes having nervous elements, the nerve cell is not different in principle from other cells but differs only in accordance with its special purpose in being provided with processes, the nerve fibres. From this point of view it was, perhaps, only to be expected that the relations between the nervous system and other organs would prove to be qualitatively of the same nature as the relations between the other, non-nervous cells, that is of chemical nature.

#### BIBLIOGRAPHY

1. LOEWI, O., AND ENGELHART, E.: *Arch. internat. de pharmacodyn. et de thérap.*, 38: 287, 1930.
2. QUASTEL, T. H., TENNENBAUM, N., AND WHEATLEY, A. H. M.: *Biochem. J.*, 30: 1668, 1936.
3. NACHMANSOHN, D., AND MACHADO, A. L.: *J. Neurophysiol.*, 6: 397, 1943.
4. MACINTOSH, F. C., AND KAHLSON, G.: *J. Physiol.*, 96: 277, 1939.
5. COWAN, S. L.: *Proc. Roy. Soc.*, 115: 216, 1934.
6. YOUNG, A. C.: *J. Neurophysiol.*, 1: 4, 1939.
7. BROWN, G. L., AND FELDBERG, W.: *J. Physiol.*, 86: 290, 1936.
8. FELDBERG, W., AND GUIMARAIS, T. A.: *J. Physiol.*, 86: 306, 1936.
9. FENG, T. P., LEE, L. Y., MENG, C. W., AND WUNG, S. C.: *Chinese J. Physiol.*, 13: 79, 1938.
10. CALABRO, QU: *Rivista di Biologia*, 15: 299, 1933.
11. BERGAMI, B.: *Atti. Accad. dei Lincei*, 6: 23, 518, 1936.
12. VON MURALT, A.: *Proc. Roy. Soc.*, 123: 399, 1937.
13. GARTEN, S.: *Handb. vergleich. Physiol.*, 1910, p. 105.
14. AUGER, D., AND FESSARD, A.: *Compt. rend. Soc. de biol.*, 128: 1067, 1938.
15. MARNAY, A., AND NACHMANSOHN, D.: *J. Physiol.*, 92: 37, 1938; 95: 29, 1939.
16. MARNAY, A., AND NACHMANSOHN, D.: *Compt. rend. Soc. de biol.*, 126: 573, 1937.
17. FELDBERG, W., FESSARD H., AND NACHMANSOHN, D.: *J. Physiol.*, 97: 2, 1939.
18. NACHMANSOHN, D., AND MEYERHOF, B.: *J. Neurophysiol.*, 4: 348, 1941.
19. NACHMANSOHN, D., AND BOELL, E. J.: *Science*, 92: 513, 1940.
20. NACHMANSOHN, D., AND STEINBACH, H. B.: *J. Neurophysiol.*, 5: 109, 1941.
21. FELDBERG, W.: *J. Physiol.*, 101: 432, 1942.
22. DEMPSEY, E. W., LISSAK, K., AND ROSENBLUETH, A.: *Am. J. Physiol.*, 128: 45, 1939.
23. CANTONI, G., AND LOEWI, O.: *J. Pharmacol. & Exper. Therap.*, 81: 67, 1944.
24. LOEWI, O.: *Pflüger's Arch. f. d. ges. Physiol.*, 206: 123, 1924.
25. NAVRATIL, E.: *Pflüger's Arch. f. d. ges. Physiol.*, 217: 610, 1927.
26. FELDBERG, W., AND VARTIAINEN, A.: *J. Physiol.*, 83: 103, 1934.
27. BROWN, G. L., AND FELDBERG, W.: *J. Physiol.*, 86: 10, 1936.
28. ELLIOTT, T. R.: *J. Physiol.*, 32: 401, 1905.
29. CLARK, A. J.: *The mode of action of drugs on cells*, London, 1933.
30. BACQ, Z. M., AND MONNIER, A. M.: *Arch. internat. de physiol.*, 40: 467, 1935.

31. MONNIER, A. M., AND DUBUISSON, A.: *Arch. internat. de physiol.*, 38: 180, 1934.
32. CANNON, W. B.: *Am. J. M. Sc.*, 198: 737, 1939.
33. HAMPEL, C. W.: *Am. J. Physiol.*, 111: 611, 1935.
34. BROWN, G. L., DALE, H. H., AND FELDBERG, W.: *J. Physiol.*, 87: 394, 1936.
35. BACQ, Z. M., AND CANNON, W. B.: *Am. J. Physiol.*, 96: 392, 1930.
36. BENDER, M. B.: *Am. J. Physiol.*, 121: 609, 1938.
37. CANNON, W. B., AND HAIMOVICI, H.: *Am. J. Physiol.*, 126: 731, 1939.
38. WARD, A. A., AND KENNARD, M. A.: *Yale J. Biol. & Med.*, 15: 189, 1942.
39. STAVRAKY, G. W.: *Tr. Roy. Soc. Canada*, 37: 127, 1943.
40. WALKER, M. A.: *Lancet*, 1: 1200, 1934.
41. HARVEY, A. M., AND LILIENTHAL, H. B.: *Bull. Johns Hopkins Hosp.*, 69: 566, 1941.
42. TORDA, CL., AND WOLFF, H. G.: *Science*, 98: 225, 1943.
43. STOERK, H., AND MARPETH, E.: *Science*, 99: 496, 1944.
44. WALKER, M. A.: *Proc. Roy. Soc. Med.*, 31: 722, 1938.
45. WILSON, A., AND STONER, H. B.: *Quart. J. Med.*, 1943, No. 49.
46. REYNOLDS, S. R. M.: *J. Physiol.*, 95: 258, 1939.
47. MACINTOSH, F. C., EMMENS, C. W., AND RICHTER, D.: *J. Physiol.*, 101: 460, 1942.
48. SOSKIN, S., WACHTEL, H., AND HECHTER, O.: *J. A. M. A.*, 114: 2090, 1940.
49. ACHESON, G. H.: *J. Nerv. & Ment. Dis.*, 100: 616, 1944.
50. LANARI, A.: *Rev. Soc. Argent. Biol.* 13: 239, 1937.

# STUDIES ON EXTRACTABLE FACTORS IN THE SPLEEN AND OTHER ORGANIC SOURCES WHICH INFLUENCE THE BLOOD PLATELET COUNT<sup>1</sup>

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Splenectomy has been employed successfully in the treatment of thrombocytopenic purpura since 1916, following Frank's suggestion (1) that this organ exerted a "myelotoxic influence" repressing platelet formation. Torrioli and his colleagues (2) testing this hypothesis, reported experimental thrombocytopenia in rabbits following intravenous injection of large doses of a protein-free aqueous extract of normal spleen. They described injury of megakaryocytes in tissue cultures of bone marrow on addition of extracts of normal spleen and other normal tissues and, particularly, the spleen of thrombocytopenic purpura (3).

By employing acetone as a solvent Troland and Lee (4) obtained highly potent extracts containing a platelet-reducing factor (thrombocytopen) from the spleens of three cases of thrombocytopenic purpura. Extracts of spleen of other types of patients and extracts of fibromyomatous uterus and of thyroid tissue yielded insignificant effects. Their results were partly corroborated by later observers although to a less striking degree, while other observers reported negative or paradoxical findings, employing for the most part the same extraction procedure. Briefly this consisted in extraction of the ground spleen in 5 volumes of reagent acetone for 6-8 weeks. The mixture was filtered and the acetone was distilled off, leaving a brownish gummy residue. The latter was suspended in distilled water and filtered. As a rule the filtrate was cloudy and orange brown. Uihlein (5) obtained clear filtrates. The fatty dark brown material remaining on the filter was discarded except in one experiment by Tocantins (6), who extracted it with ether and injected an aqueous suspension of the dried residue intravenously, reporting negative results.

The active principle (thrombocytopen) has been demonstrated in the spleen of certain cases of purpura hemorrhagica (5, 7, 8, 9, 10, 11), hemolytic icterus (5), chronic malignant leukopenia with thrombocytosis (12) and in normal spleen (7) but was not demonstrated in other normal spleens (4, 5, 10, 11), in the spleens of other cases of purpura hemorrhagica (5, 6, 11, 12, 13, 14, 15, 16) and hemolytic icterus (4, 5, 10), and in spleens from Hodgkin's disease (5), leukemia (10, 11), chronic passive congestion and Banti's disease (4, 5, 6, 10, 11) and other conditions (8, 10). The extract from one case of purpura increased the blood platelets (11). Hobson and Witts (7) obtained a more striking effect with an emulsion of normal spleen in Ringer's solution than with an acetone extract of normal spleen or of a case of purpura.

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## EXPERIMENTAL OBSERVATIONS

The spleen of a patient with classical chronic thrombocytopenic purpura was prepared for extraction by the method of Troland and Lee (4). The spleen, which weighed 287 grams, showed reticulum cell hyperplasia in small clusters and nodules, especially about Malpighian follicles, with vacuolization of cytoplasm suggestive of fat-like inclusions, confirmed by Sudan stain. The ground spleen was extracted with five volumes of reagent acetone for a prolonged period and filtered. The acetone was distilled off, leaving a brownish gummy residue weighing 3.42 gm. Part of this (2.7 gm) was shaken with distilled water, filtered, and the cloudy filtrate injected intravenously into a rabbit as in the Troland-Lee procedure, but given in 10 doses at 8 hour intervals instead of in a single dose. Thrombocytopenia was maintained for the entire period (fig. 1A). The non-filterable residue of this material suspended in peanut oil was injected intramuscularly in divided doses for 7 days; compared with the intravenous doses, it proved far more potent in the degree and duration of thrombocytopenia produced (fig. 1B). One fifth of the original acetone extract (0.684 gm.) was shaken with ether instead of water and the ether-soluble fraction (0.553 gm.) injected in peanut oil. It proved highly potent, equalling in its effect the combined results of all the preceding injections (fig. 1C). It was then discovered that suspending the active materials in distilled water or saline for intramuscular injection resulted in much greater and more consistent response than in the peanut oil vehicle despite their water-insolubility (fig. 1D). The water-soluble fraction, weighing 66 mg., was inert (fig. 1E).

Thrombocytopen was demonstrated in the normal spleen, although in much smaller amounts than in that of purpura. Several rabbits were standardized with 50 mg. doses in saline.

*Thrombocytosis-producing factor (thrombocytosin).* Extracts of the spleen of a case of Hodgkin's disease yielded sharp elevation of platelet counts on preliminary tests. The masking effect of fat-soluble antagonists to thrombocytopen, e.g., the thrombocytosis-producing factor of Schiff and Hirschberger (17), was suspected and separation was accomplished by methods involving fractional solution and fractional crystallization. Methanol (absolute methyl alcohol) proved a most satisfactory solvent.

Thrombocytopen was demonstrated in the less soluble fraction (cold methanol) and in the first harvest of crystals obtained from methanol solution on slow evaporation. The thrombocytosis-producing factor, subsequently termed *thrombocytosin*, was demonstrated in the readily soluble fraction and in crystals formed on further evaporation. Crude separation was also achieved by suspending the primary acetone-ether extract in saline; thrombocytosin was contained in the milky dispersion which passed the filter; thrombocytopen was left on the filter and formed a flocculent suspension in saline.

In a few instances discordant results were obtained which suggested imperfect separation of the mutually antagonistic factors. A convenient separation procedure for analysis of spleen and other materials was eventually achieved through



emulsification with alkali. The primary residue from acetone extraction was shaken with ether, filtered and evaporated. The ether-soluble residue was shaken with weak sodium hydroxide solution and kept in a warm room or incubator 12-24 hours, then acidified with a slight excess of hydrochloric acid and extracted with ether in a separatory funnel. The ethereal solution was evaporated to dryness, the residue was re-extracted with acetone, dried, weighed, then

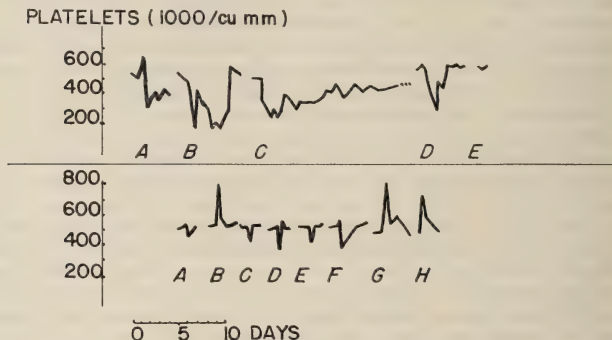


FIG. 1. (Top) Effects of extracts of spleen of purpura hemorrhagica on platelet count in rabbits:

- Troland-Lee extract (filtered aqueous suspension) given in 10 intravenous doses;
- Non-filter-passing residue of above in peanut oil intramuscularly in 10 doses;
- Ether-soluble fraction in peanut oil in single dose intramuscularly;
- Unmeasured small dose of above (estimated at less than 10 mgm.) in aqueous suspension intramuscularly;
- Water-soluble fraction (ether-insoluble) in aqueous solution intramuscularly.

FIG. 2. (Bottom) Effects of extracts of normal bovine spleen:

- 50 mgm. of slow-dissolving fraction (in methyl alcohol) of acetone-ether-soluble extract;
- 50 mgm. of quick-dissolving fraction (in same rabbit).
- c) and d) 20 mgm. of unfractionated ether-acetone-soluble portion of saponified primary extract injected into separate rabbits;
- e) 5 mgm. of first yield of crystals from methyl alcohol solution of above mixture.
- f) 20 mgm. of same;
- g) 5 mgm. of second yield of crystals;
- h) 20 mgm. of same.

redissolved in methyl alcohol and set aside at room temperature to evaporate slowly. As crystals formed on the side of the beaker the mother liquor was decanted for a similar period of evaporation into each of several other evaporation beakers in succession until only an amorphous product was obtained. In some instances recrystallization was found necessary to obtain colorless crystals. A low-power loupe was employed in grouping crystals of like type. These were pooled in ether solution, weighed following evaporation of ether in a previously weighed Erlenmeyer flask, redissolved in acetone to make up separate doses

of known amount for assay, and added to 10 cc. quantities of sterile 0.85 per cent saline. The acetone was distilled off in vacuo at 40°C. until no trace of its odor could be detected. The resulting cloudy or flocculent suspension was shaken thoroughly before injection. In Figure 2 are shown the comparative potencies of fractions obtained from bovine spleen.

By this procedure fractions of surprising potency were secured, exhibiting marked thrombocytosin or thrombocytopen activity in doses of 5 mg. (Fig. 2E, F, G, H). Further purification was subsequently achieved following the demonstration by Dr. Harry Sobotka that the crystalline material consisted largely of pure cholesterol upon which the active factors had become adsorbed. The procedure which was employed consisted in vigorous saponification of the crude ether extract in boiling alcoholic potassium hydroxide solution. Virtually all the cholesterol separated out as crystals when the mixture was permitted to stand overnight in the refrigerator; bioassay of these crystals revealed their complete inactivity. Fatty acids were then removed by addition of barium chloride and also showed absence of activity following their recovery from the insoluble barium soaps. The active principles were recovered from the residual clear solution by ether extraction. The material obtained was oily, noncrystalline, and had a distinctly fishy odor. Purified thus, both factors could be precipitated partly or completely on addition of digitonin and could be recovered from the insoluble digitonide in active form. From these data the impression has been gained that both active principles may be steroids; further studies are contemplated to confirm this. Studies are now in progress which point to the possible development of a procedure of separation and purification based on the principle of differential adsorption on aluminum oxide and magnesium silicate (chromatographic adsorption). Following the demonstration that both factors are stable under prolonged heating and exposure to alkali, air, light, or drying, their extraction from the original organic sources was greatly expedited, employing such methods as continuous reflux extraction with boiling acetone in Soxhlet apparatus employing powdered dried raw material.

Upon injection into rabbits thrombocytopen produced a fall in platelets roughly proportional to the doses given within certain limits (fig. 2E, F), although after prolonged administration for several days in large doses a refractory state and "platelet escape" occurred and the bone marrow revealed a remarkable hyperplasia of megakaryocytes in various stages of maturation. In contrast thrombocytosin produced maximal effects or near maximal effects in doses of 5 mg. (fig. 2G) equalling the effect of 20 mg. (fig. 2H) or more, suggesting the action of protective mechanisms. Rabbits differed moderately in their respective sensitivity to each factor. No evidences of toxicity were detected with physiologically effective doses given repeatedly on alternate or successive days for periods of a week or longer. There were no significant changes in erythrocyte or leukocyte count. Purpura was not observed in any of the experiments with thrombocytopen although prolongation of bleeding time persisted for weeks following a large dose in peanut oil (fig. 1C). Excessive agglutination of platelets and clotting of blood in the counting pipette occurred in some experiments with thrombocytosin

at or near the peak of platelet rise; thromboses were not observed. Sensitivity to each factor was preserved undiminished after repeated tests with single doses; one of the rabbits received 26 injections of either factor in  $4\frac{1}{2}$  months and another received 31 injections and 10 oral doses in the same period.

With the establishment of effective methods of separation, numerous analyses were undertaken for each factor in normal beef spleen, in human spleen from various conditions (aplastic anemia, Hodgkin's disease, monocytic leukemia), in normal human liver, brain, lymph nodes, omentum, bone marrow, heart, subcutaneous fat and perirenal fat (cases of accidental or sudden death), and in egg yolk, peanut oil, butter and soap. Urine of normal males and of certain patients was titrated by the same procedure after initial evaporation to dryness of the 24 hour sample in vacuo.

The concentration of each factor in the material analyzed was calculated from the results of bioassays, employing as the unit of comparison the dosage required to produce a peak increase or decrease of 100,000 platelets. The calculations are subject to criticism for several reasons such as 1) the incompleteness of some of the extractions, 2) the differences in reactivity of test animals and 3) (in earlier experiments) imperfect separation of the two (oppositely acting) factors. The incomplete tabulation which follows has therefore only suggestive value.

| ASSAY MATERIAL   | THROMBOCY-<br>TOPEN | THROMBOCY-<br>TOSIN |
|--|---------------------|---------------------|
|  | (units/gram)        | (units/gram)        |
| Normal human spleen (4 cases).....                               | 0.70±               | 0.24                |
| Normal beef spleens (pooled).....                                | 0.35                | 0.25                |
| Spleen, Hodgkin's disease (2 cases).....                         | 0.0-0.16            | 0.07-1.6            |
| Spleen, aplastic anemia, hemosiderosis.....                      | 0.14                | 0.11                |
| Spleen, monocytic leukemia.....                                  | 0.007               | 0.003               |
| SPLEEN, PURPURA HEMORRHAGICA                                     |                     |                     |
| Brain tissue.....  | 7.0+                |                     |
| Liver.....   | 0.0                 | 0.006               |
| Lymph node.....  | ?                   | 6.1                 |
| Bone marrow.....   | 0.0                 | 0.0                 |
| Subcutaneous fat.....  | 0.0                 | 2.0                 |
| Perirenal fat.....   | 0.0                 | 0.0                 |
| Peanut oil.....  | 0.0                 | 0.0                 |
| Egg yolk.....  | 0.1+                | 1.6±                |
| Normal male urine (4 subjects) (unit output/24 hr.).....         | 1.8                 | 0.7-34.3            |
| Urine, splenectomy for aplastic anemia (unit output/24 hr.)..... | 0.0                 | 427.0               |

The findings given above suggest tentatively that in the human organism significant amounts of both thrombocytopen and thrombocytosin occur in the spleen, diminishing in amount with metaplasia or replacement of its functioning reticulo-endothelial elements (hemosiderosis, Hodgkin's disease, leukemia). The marked excess of thrombocytopen and the histologic findings in the spleen of chronic purpura support the concept of hypersplenism as its basis.

Preliminary assays of lymph nodes gave equivocal results for thrombocytopen but demonstrated thrombocytosin in great abundance.

Egg yolk proved rich in both thrombocytopen and thrombocytosin. The proportions were not uniform; in most tests the injected crude primary acetone-ether extracts exerted a thrombocytosin effect predominantly, also on oral administration. Two patients with advanced leukemia and thrombocytopenia were treated with this oral preparation and suffered no impairment of appetite or other observable ill effect; both patients displayed coincidental elevation in platelet count almost to the normal level. Comparable effects were obtained with whole egg yolk, confirming observations of Schiff and Hirschberger (17), who obtained similar effects also with some brands of sesame oil.

The urinary output of both factors in normal males varied widely. In a splenectomized patient thrombocytopen was not demonstrable, whereas thrombocytosin appeared in enormous amount.

#### DISCUSSION

The premise appears warranted that the spleen exerts a dual control on the rate of delivery of platelets into the circulating blood. The ineffectiveness of increased dosage of thrombocytosin above a narrow range (about 5 mg. in the rabbit) and its high level of excretion in the urine following splenectomy are evidences for the dominant role of the spleen in inactivating surpluses absorbed from the diet. How this is accomplished is not apparent; the high concentration of thrombocytosin in spleen and in lymph nodes and its virtual absence in liver, brain, and other tissues tested suggest its selective accumulation within the cells of the general reticulo-endothelial system as the preliminary stage of its inactivation.

The marked abundance of thrombocytopen in the spleen of chronic thrombocytopenic purpura indicates the important role of the spleen in producing a platelet-suppressing hormone. Whether or not thrombocytopen is synthesized by its reticulum cells from prosthetic substances furnished by the diet (e.g., eggs) and the possible adjunct role of lymph nodes remain to be determined.

The high content of thrombocytosin in subcutaneous fat contrasts sharply with its virtual absence in perirenal fat and possibly indicates differences in their biological behavior. The suggestion is offered that the elevation of platelet count commonly found after surgical operations or other trauma (18) is caused by mobilization of stored thrombocytosin from traumatized fat cells.

The distribution and physical characteristics of the two factors are such that thrombocytosin may be tentatively classified as a fat-soluble diet factor and thrombocytopen as a fat-soluble hormone. Both have certain physico-chemical properties which suggest the possibility of their steroid nature although definitive proof is still lacking.

Application in therapy is suggested for thrombocytosin in certain cases of "idiopathic" or secondary thrombocytopenic purpura, and for thrombocytopen in states of hypercoagulability of the blood, in thrombocythemia (19) and possibly in vegetative endocarditis.

## SUMMARY

Thrombocytopen, a platelet-lowering lipid, and thrombocytosin, a platelet-elevating lipid, exist in the spleen in comparative abundance and may be isolated in relatively concentrated form adsorbed on cholesterol following crystallization of the latter from crude acetone-ether extracts, previously emulsified, dissolved in absolute methyl alcohol. Preliminary data suggest that both are steroids. In purpura hemorrhagica the spleen may exhibit lipoidal vacuolization of the hyperplastic reticulum cells and thrombocytopen may be extracted in great quantity. Thrombocytosin is apparently stored in subcutaneous adipose tissue and its mobilization from traumatized fat cells may possibly explain elevations in platelet count after surgical operation. Both factors are also present in egg yolk, thrombocytosin predominating and effective orally. The purified factors are apparently nontoxic. Possible therapeutic applications are suggested. The hypothesis is offered that the spleen controls the level of blood platelets both by production of thrombocytopen and, together with other elements of the reticulo-endothelial system, by inactivation of surplus thrombocytosin absorbed from the diet. The histological findings and results of bioassay of the spleen in chronic thrombocytopenic purpura favor hypersplenism as its basis. Urinary titration for both factors may indicate to some extent the state of splenic function.

## REFERENCES

1. FRANK, E.: Die essentielle Thrombopenie. *Berl. klin. Wchnschr.*, 52: 454, 490, 1915.
2. TORRIOLI AND PUSIC, cited by TORRIOLI AND PUDDU (reference 3).
3. TORRIOLI, M., AND PUDDU, V.: Recent Studies on the Pathogenesis of Werlhof's Disease. *JAMA.*, 111: 1455, 1938.
4. TROLAND, C., AND LEE, F.: A Preliminary Report on a Platelet-Reducing Substance in the Spleen of Thrombocytopenic Purpura. *Bull. Johns Hopkins Hosp.*, 62: 85, 1938.  
—: Thrombocytopen: A Substance in the Extract from the Spleen of Patients with Idiopathic Thrombocytopenic Purpura that Reduces the Number of Blood Platelets. *JAMA.*, 111: 221, 1938.
5. UHLEIN, A.: Effect of Injection of Tissue Extracts on the Number of Blood Platelets. *J. Lab. & Clin. Med.*, 28: 157, 1942.
6. TOCANTINS, L. M.: No Platelet-Destroying Action in Extracts of the Spleen and Urine of Patients with Chronic Thrombopenic Purpura. *Proc. Soc. Exper. Biol. & Med.*, 42: 485, 1939.
7. HOBSON, F. C. G., AND WITTS, L. J.: Platelet-Reducing Extracts of the Spleen. *Brit. Med. J.*, 1: 50, 1940.
8. ROSE, HUGH, JR., AND BOYER, L. B.: Thrombocytopen: A Confirmatory Report. *J. Clin. Invest.*, 20: 81, 1941.
9. OTENASEK, F., AND LEE, F. C.: Further Observation on Thrombocytopen. *J. Lab. & Clin. Med.*, 26: 1266, 1941.
10. PAUL, J. T.: The Effect of Splenic Extracts from Cases of Essential Thrombocytopenic Purpura on the Platelets and Hematopoietic Organs of Rabbits. *J. Lab. & Clin. Med.*, 27: 754, 1942.
11. MAJOR, R. H., AND WEBER, C. J.: Is There a Platelet-Reducing Substance in the Spleen of Thrombocytopenic Purpura? *J. Lab. & Clin. Med.*, 25: 10, 1939.
12. CRONKITE, P.: Further Studies of Platelet Reducing Substances in Splenic Extracts. *Ann. Int. Med.* 20: 52, 1944.



13. POHLE, F. J., AND MEYER, O. O.: Inability to Demonstrate a Platelet Reducing Substance in an Acetone Extract of the Spleen from Patients with Idiopathic Thrombocytopenic Purpura. *J. Clin. Invest.*, 18: 478, 1939.
14. HODGE, I. G., AND STRONG, P. T.: The Effect of Splenic Extracts of Patients with Thrombocytopenic Purpura on the Platelet Count of Rabbits. *Bull. Ayer. Clin. Lab., Pennsylvania Hospital*, 3: 267, 1939.
15. COLMER, M. L., AND MERSHEIMER, W. L.: Relation of Splenic Extracts to Etiology of Essential Thrombopenia. *Arch. Surg.*, 43: 422, 1941.
16. MOORE, C. V.: Abstract of Discussion on Paper by Limarzi and Schleicher. The Reaction of Peripheral Blood and Bone Marrow in Chronic Hemorrhage and in Essential Thrombopenic Purpura, *JAMA.*, 114: 12, 1940.
17. SCHIFF, E., AND HIRSCHBERGER, C.: Thrombocytosis Produced by a Hitherto Unknown Substance, The "Fat-Soluble T Factor," *Am. J. Dis. Child.*, 53: 32, 1937; Ueber den T-Faktor. *VII. Jahrb. f. Kinderheilk.*, 150: 247, 1937.
18. STEINER, P. E., AND GUNN, F. D.: Effect of Splenectomy and of Other Surgical Procedures Upon Circulating Blood Platelets (Rabbits), *Proc. Soc. Exper. Biol. & Med.*, 28: 1088, 1931.
- WRIGHT, H. P.: Changes in the Adhesiveness of Blood Platelets Following Parturition and Surgical Operation, *J. Path. & Bact.*, 54: 461, 1942, (cited by Adams).
- ADAMS, ELIJAH: Postoperative Thrombocytosis, *Arch. Int. Med.*, 73: 329, 1944.
19. ROSENTHAL, N.: Hemorrhagic Diatheses, in *Handbook of Hematology*, edited by Hal Downey. Paul B. Hoeber, Inc., New York, 1938, vol. 1, section 8, pp. 497-551.

## CORRELATIONS BETWEEN THE ELECTROENCEPHALOGRAM AND THE HISTOLOGICAL STRUCTURE OF GLIOGENOUS AND METASTATIC BRAIN TUMORS<sup>1</sup>

L. GREENSTEIN, M.D., AND HANS STRAUSS, M.D.

As early as 1929 Berger (1) showed that a brain tumor modifies the electrical activity of the brain as recorded by the electroencephalogram. In 1936 Walter (2) demonstrated more or less continuous slow activity in the neighborhood of a tumor and the possibility of localizing the lesion by finding the region in which this activity was maximal. In 1938 Williams and Gibbs (3) stated that by correlating the frequency and amplitude of the pathologic waves with the position of the discharge and its extent, it was possible in some cases to surmise the nature of the lesion. Strauss (5) reported that as a rule gliogenous tumors show a higher degree of abnormality in the electroencephalogram than other types of tumors. With this latter thought in mind a more detailed survey of electroencephalographic records of the various types of primary neuroectodermal tumors and metastatic carcinomatous lesions was undertaken in the hope that some further knowledge might be obtained as to the existence of any correlation between the degree of EEG abnormality and the specific pathological nature of the tumor.

### METHOD

Only cases were considered in which a pathological diagnosis was made either at postmortem examination or by histological examination of a biopsy specimen. Only supratentorial lesions were considered and fifty-five such records were taken from the electroencephalogram laboratory of The Mount Sinai Hospital. These cases were thoroughly studied from a pathological point of view in the neuropathology laboratory (Dr. J. H. Globus). Of the total number of records, eight were metastatic carcinomatous lesions, and the remaining forty-seven were primary neuroectodermal tumors.

In discussing the gliogenous or primary neuroectodermal tumors, their relative malignancy as measured by their rapidity of growth and stage of cell development will be designated according to Globus's classification (4) and terminology (fig. 1). In assaying the relative malignancy of any primary neuroectodermal neoplasm, one may safely state that tumors made up of poorly differentiated cell forms of either neuroblastic or spongioblastic derivation are primarily capable of more rapid growth and proliferation than those containing a more highly differentiated cell form. In between these extremes are intermediate or transitional stages of cell differentiation and growth and these are so designated as the transitional type of gliogenous tumor. The metastatic lesions were simply termed metastatic carcinomatous lesions and no attempt was made either to determine the primary site or to differentiate one type of carcinomatous lesion from another.

We used a three channel Grass electroencephalogram machine with the fol-

<sup>1</sup> From the Neurological Service of Dr. I. S. Wechsler, The Mount Sinai Hospital, New York, N. Y.

lowing eleven electrodes: vertex (placed in the midline halfway between the nasion and the inion), two "indifferents" (placed on the lobes of the right and left ear), four pairs of symmetrical electrodes above the hemispheres, namely, two frontal electrodes (placed halfway between the nasion and the vertex and 4 cm. on either side of the midline), 2 central electrodes (placed 4 cm. lateral to the vertex electrode), 2 parietal electrodes (placed 4 cm. behind the vertex and 7 cm. on either side of the midline) and 2 occipital electrodes (placed 3 cm. in front of the inion and 3 cm. on either side of the midline). Records from symmetrical electrodes were taken simultaneously and the following leads were employed: fronto-occipital, fronto-indifferent, fronto-vertex, centro-vertex, parieto-vertex,

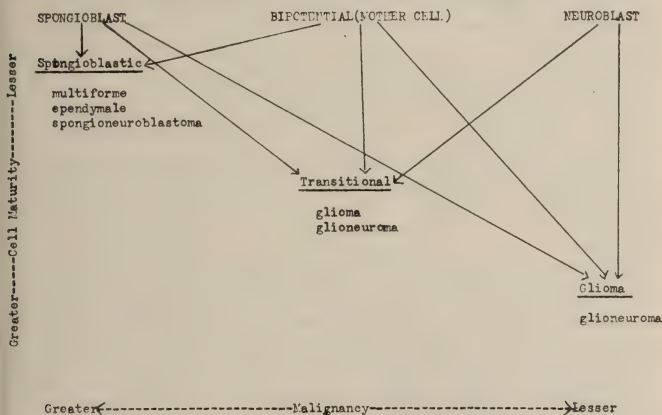


FIG. 1. Classification of neuroectodermal tumors and their relative malignancies (Globus).

occipito-vertex, centro-indifferent, parieto-indifferent, occipito-indifferent, fronto-central, centro-parietal, parieto-occipital. The procedure used for making measurements and for the localization of the intracranial lesions was described in a previous paper (5). The per cent time delta which is the percentage of total length of record occupied by delta activity was determined for each lead with at least 100 cm. of record of each lead being measured. Only potentials with a frequency of six cycles or less per second and a voltage of at least 20 microvolts were considered as delta waves. All the leads used were bipolar including those connecting with the so-called indifferent electrodes, which we do not consider indifferent since they record potentials from the temporal lobes.

The criterion used for correlating our observation in the electroencephalogram with the pathological nature of the lesion was the focal per cent time delta. To obtain this figure we had to divide the sum of the per cent time delta for all the

various leads connecting with one or more electrodes (localizing the site of the lesion) by the sum of the number of leads. The result so obtained represented the focal per cent time delta.

In figure 2, the lesion is localized at the right frontal region since all the leads having the right frontal electrode in common show the maximal amount of delta activity. To obtain the focal per cent time delta, the sum of the per cent time

| Lead.....   | FO | FV | CV | PV | OV | FI | CI | PI | OI | FC | CP | PO |
|-------------|----|----|----|----|----|----|----|----|----|----|----|----|
| Right ..... | 60 | 42 | 0  | 11 | 10 | 55 | 25 | 29 | 10 | 44 | 7  | 23 |
| Left.....   | 35 | 23 | 0  | 0  | 6  | 27 | 20 | 5  | 0  | 10 | 0  | 0  |

FIG. 2. Delta index for all the leads in a case of metastatic carcinoma

C—central  
F—frontal  
I—indifferent  
O—occipital  
P—parietal  
V—vertex.

| PATHOLOGICAL FINDINGS | TOTAL<br>NO. OF<br>CASES | DELTA INDEX    |      |       |                |                |       |                |
|-----------------------|--------------------------|----------------|------|-------|----------------|----------------|-------|----------------|
|                       |                          | 0              | 0-10 | 10-20 | 20-30          | 30-40          | 40-50 | 50 or<br>more  |
| Spongioblastic .....  | 20                       |                |      |       | 3 <sup>1</sup> | 2              | 4     | 10             |
| Metastatic .....      | 8                        | 1 <sup>2</sup> |      |       |                |                | 2     | 5              |
| Transitional .....    | 23                       | 3 <sup>3</sup> |      | 3     | 6              | 5              | 1     | 5 <sup>4</sup> |
| Glioma .....          | 4                        |                |      | 1     | 1 <sup>5</sup> | 1 <sup>6</sup> |       | 1 <sup>7</sup> |

FIG. 3: Focal delta index in 55 cases of gliogenous and metastatic tumors

<sup>1</sup> Possessed elements seen in transitional gliomas.

<sup>2</sup> Normal record.

<sup>3</sup> All three cases had normal records.

<sup>4</sup> Three of the five cases had a spongioblastic orientation.

<sup>5</sup> Probable case of tuberous sclerosis.

<sup>6</sup> Diagnosed as a probable spongioneuroblastoma.

<sup>7</sup> Possessed spongioblastic elements.

delta of all the leads connected with the right frontal electrode is divided by the number of such leads. In the case cited in figure 2:

$$\begin{array}{cccc} \text{FO} & \text{FV} & \text{FI} & \text{FC} \\ 60 & + & 42 & + & 55 & + & 44 \end{array}$$

the sum is 201. The focal per cent time delta would therefore be  $201/4$  or 50. The same procedure was followed with all of the 55 cases.

#### RESULTS

In the spongioblastic group (fig. 3) fourteen of the twenty cases had a focal per cent time delta of 40 or more. Of the remaining six having a focal per cent time delta of less than 40, one on histological examination possessed elements seen in the transitional group of primary neuroectodermal tumors. The correct percentage of this group having a focal per cent time delta of 40 or more would then be  $14/19$  or 74 per cent. In no instance was a normal record obtained in this series.

In the transitional group of 23 cases, fourteen had a focal per cent time delta of less than 40, 3 cases had a normal record, and the remaining 6 cases had a focal per cent time delta of 40 or more. Of these last 6 cases, 4 on histological examination were found to possess spongioblastic orientation. The correct percentage of this group having a focal per cent time delta of 40 or more would therefore be  $\frac{4}{17}$  or 10 per cent.

There were 4 cases of simple glioma or glioneuroma. One case had a focal per cent time delta of 40, one between 30 and 40, and both of these cases on histological examination had spongioblastic orientation. Of the other two cases, one had focal per cent time delta of between 20 and 30 and this case on histological examination seemed to be a probable case of tuberous sclerosis. The remaining case had a focal per cent time delta of less than 20. In short, none of the well-differentiated gliomas had a focal per cent time delta of 40 or more.

Of the 8 cases comprising the metastatic carcinomatous group, 7 or  $87\frac{1}{2}$  per cent had a focal per cent time delta of 40 or more. The remaining case had a normal record.

No correlation was found to exist between the focal per cent time delta and the site or extent of the tumor. The only correlation was found to depend upon the pathological nature of the lesion.

#### SUMMARY

1. An attempt was made to correlate the degree of electroencephalographic abnormality with the pathological nature of primary neuroectodermal and metastatic carcinomatous tumors.

2. Fifty-five cases having a pathological histological diagnosis and an electroencephalogram record constituted the material used.

3. Seventy four per cent of spongioblastic tumors had a focal per cent time delta of 40 or more; whereas only 10 per cent of the transitional group had a focal per cent time delta of 40 or more and none of the well-differentiated gliomas had a focal per cent time delta of 40 or more.

4. The results seem to indicate that a focal per cent time delta of 40 or more is strongly indicative of a spongioblastic or metastatic carcinomatous tumor.

5. These findings may be of practical aid to the neurosurgeon in indicating the type of tumor to be expected in the operation.

#### BIBLIOGRAPHY

1. BERGER, H.: Ueber das Elektroencephalogramm des Menschen. I Mitteilung, Arch. f. Psychiat., 87: 527, 1929.
2. WALTER, W. G.: The location of cerebral tumors by electroencephalography, Lancet, 2: 305, 1936. Electroencephalogram in cases of cerebral tumor. Proc. Psy. Soc. Med., 30: 579, 1937.
3. WILLIAMS, D., AND GIBS, F. A.: Localization of cerebral lesions by electroencephalography, Am. Neurol. A., 64: 130, 1928 (a); The localization of intracranial lesions by electroencephalography, New England J. Med., 218: 998, 1938 (b).
4. GLOBUS, J. H., AND KUHLENBECH, H.: Tumors of the Striato-Thalamic and Related Regions, Arch. Path., 34: 674, 1942.
5. STRAUSS, HANS: A method for differential diagnosis of abnormal electroencephalograms, J. Mt. Sinai Hosp., 9: 1, 17, 1942.



## REMINISCENCES 1900-1937

ROBERT T. FRANK, M.D.

At midnight in May 1898, Dr. Joseph Brettauer, then adjunct gynecologist, telephoned me (a third year medical student), inviting me to watch him perform a cesarean section. A few minutes later I joined him at the entrance to the old Mount Sinai Hospital located at 67th Street and Lexington Avenue. This was my first contact with the Hospital with which I since have been connected for forty-five years.

We walked through the long gloomy hall to take the elevator, a huge platform with rope controls. The patient, who had just arrived, was wheeled onto the lift; the old night orderly pulled the rope and slowly we ascended. The mechanism was such that the platform jumped and shivered and shook, as it rose, sufficiently to dislodge even well fitted dentures. As we reached the operating floor, the patient shrieked and writhed. The jolts had precipitated the birth; cesarian section proved unnecessary.

My next contact occurred two years later—the momentous day of examination for interns and externs. I joined a large group of worried, excited and feverish senior medical students, the prospective candidates. For two hours we wrote frantically, trying to answer the written questions. Next day at noon, we eagerly scanned the bulletin board. My name was among the forty survivors for oral and practical examinations.

Of the nightmare that followed, I recall the genial informal queries posed by handsome Howard Lilienthal. This seemingly was a mere chat with a youthful colleague, but, in retrospect, proved a searching analysis of background, education and knowledge. Then a session with imposing Dr. Barney Sachs—a soul searching ordeal covering every aspect of medicine—conducted systematically, slowly and fairly. Finally entry into the lion's den, presided over by the red-bearded Dr. Rudisch, a gruff, grim and thickset individual, the perfect image of an old sea captain. He asked me to examine a patient in whom I found a large mass in the upper left abdominal region. "What is the diagnosis and on what do you base your conclusion?" was his question. I decided that this was a kidney tumor and gave the reason upon which I based this diagnosis. Rudisch, none too gently told me that I was wrong, that the mass was a spleen. He frowned portentously, refused to listen to further discussion, and, as I found out later, "marked me down" heavily. Consequently when the list of successful candidates appeared, my name was that of the lowest extern, a one year position.

The sequel occurred some six weeks later, when as anesthetist I assisted at the operation of this same patient. Dr. Rudisch was present; Dr. Arpad Gerster, the senior attending surgeon made his usual long incision, exposing the growth. A mere glance, and he rumbled in his *basso profundo*, "Rudisch, you are wrong, this is a kidney tumor." This little difference of opinion, cost me an extra year on the house staff, three and one-half instead of two and one-half years, a loss or

I have dwelt such a long time on this point since nowhere have I found this second important function of the nerve even mentioned.

In what main direction does the discovery of the neurochemical mechanism increase our knowledge? To my mind the most important advance is that at least the old classical problem concerning the nature of the transmission of the excitation from nerve to its effector organ has been conclusively answered. By the proof that this transmission is effected by substances liberated by the nervous system, at the same time the first evidence has been given that the nervous system is not only the effector organ for chemical influences and not only shares the general metabolism of the body, but that, by itself, it exerts specific chemical actions in the organism.

Of almost equal importance it seems to me is the disclosure of the nature of peripheral inhibition. Hitherto, it has been impossible to conceive how stimulation of nerves could lead to an inhibition of activity in the effector organs. Now we know that this condition is brought about by release of chemical inhibitors the matter is explained and appears, indeed, to be self-evident. Since we know that the process of excitation in the nerve is unspecific up to a certain point, there remains, I believe, no possibility whatever of imagining how nerve stimulation can inhibit an organ otherwise than by chemical means. In other words, the chemical mechanism is the only conceivable mechanism of peripheral inhibition.

The disclosure of the nature of peripheral inhibition is important also from the following point: the fact that transmitters are liberated by the stimulation both of so-called augmentory nerves whose effect is augmentation of function and of inhibitory nerves whose effect is inhibition of function proves that, whether the stimulation be augmentory or inhibitory in its ultimate effect, the direct effect is always an increase in functional activity so far as the direct point of attack, that is the nerve ending, is concerned.

The discovery of the chemical transmission and all that is connected with it thus far has not brought about many practical consequences for the insight into and the treatment of diseases. One, of course, never knows what the future still may bring. Thus far there exists, as you know, only one disease, the myasthenia gravis, where the investigation of the mechanism of the prostigmine treatment starting from the knowledge obtained by the new facts has contributed to the insight into the mechanism of this disturbance.

It had been known for a long time that eserine is able to overcome the action of small doses of curare, which consists in a depression of the responsiveness of the motor endplates to nervous stimulation. It was the resemblance of the myasthenic syndrome to that of a light curare poisoning which in 1933 suggested to Dr. Mary Walker (40) the use of eserine in myasthenia. Since this proved to be so successful it seemed likely that in the myasthenic disturbance a depression of the responsiveness of the motor endplates to nervous stimulation, similar to that provoked by curare, is involved. Not only eserine or prostigmine respectively but Ac.Ch. too counteracts light curare poisoning. Hence it seems likely that the curative action of eserine or prostigmine is due to their antiesterasic power making more Ac.Ch. available. The assumption that in myasthenia there

exists a curare-like depression of the sensitivity of the motor endplates to Ac.Ch. released by nervous stimulation later on seemed to be invalidated by the contention of Harvey (41) that the myasthenic muscle is exquisitely sensitive to Ac.Ch.; the partially curarized muscle is less sensitive than normal muscles. Hence Harvey suggested that the myasthenic disturbance might consist in a failure of the nerve to release on stimulation a normal quantum of Ac.Ch. This failure could for instance be caused by a decreased ability of the nerve of synthesizing Ac.Ch. As a matter of fact Torda and Wolff (42) reported that the synthesis of Ac.Ch. by frog's brain was less in presence of myasthenic serum than in the presence of normal serum. The results were at variance with those obtained later on by Stoerk and Mapeth (43), who instead of frog's brain used rat's brain. Be that as it may. At any rate the results of Harvey's experiments confirming previous ones of Lanari (50), which we now have to discuss, do not need for their interpretation the hypothesis that the release of Ac.Ch. from stimulated myasthenic nerves is inadequate. Harvey injected intra-arterially the same rather large dose of Ac.Ch. or prostigmine respectively to normal and to myasthenics. The effect was that in the normal subject there was produced a motor paralysis, in the myasthenic a strong contraction. By the way Acheson (49) using much smaller doses of Ac.Ch. was so far not able to find a significant difference in the reaction of the muscles of normal and myasthenic subjects. How could Harvey's results be interpreted? It is well known that Ac.Ch. stimulates at relatively low concentrations and depresses at high concentrations. The fact claimed by Harvey that the same dose of Ac.Ch. which already paralyzes in the normal only stimulates in the myasthenic can in my opinion be interpreted only in such a way that the responsiveness of the motor endplate in the myasthenic is decreased. This assumption is in harmony with the view that there may be present in the myasthenic a curarizing agent, that means an agent which depresses the sensitivity of the motor endplate to Ac.Ch. whether released from the nerve or applied from without. At this point I have to quote experiments strongly supporting the view that a curarizing agent is produced and acts within the myasthenic. Here again Dr. Mary Walker (44) did pioneer work in 1938. She occluded for a while the circulation in the upper limbs of myasthenics and exercised the muscles of the forearm. On releasing the constriction an almost immediate increase in the clinical signs, for instance drooping of the eyelids, was observed. Quite recently Wilson and Stoner (45) registering the changes produced confirmed Walker's observations and went a step further. They withdrew blood from the compressed exercised limb of myasthenics and investigated the effect of the serum on nerve muscle preparations of frogs. They claim to have found that the effect of indirect stimulation after a short while considerably decreased or even vanished whereas the effect of direct stimulation did not decrease at all. In other words the nerve muscle preparation reacted to the myasthenic serum exactly as to curare.

In summarizing I should like to say that quite a few of the experiments quoted are apparently consistent with the view that within the myasthenic an agent is produced presumably in the muscle which depresses the sensitivity of the motor endplate to Ac.Ch. released from the nerve endings or applied from without and

The significance, both immediate and remote, of the publication of William Harvey's (1578-1657) *De Motu Cordis* in 1628, needs no further enlargement here. The distinguished founder of modern physiology, whose discovery forms the cornerstone of all medical thinking, comes into our studies in an entirely different rôle, that of pathologist. On November 14, 1635, Harvey was called



*The Old, Old, very Old Man or Thomas Parr, the Sonne of John Parr of Winnington in the Parish of Alderbury. In the County of Shropshire who was Borne in 1483 in The Raigne of King Edward the 4<sup>th</sup> and is now living in The Strana, beinge aged 152 yeares and odd Monethes 1635 He dyed November the 15<sup>th</sup> And is now buried in Westminster 1635.*

FIG. 2. Thomas Parr (1483-1635), most famous of the supercentenarians. (Reproduced from print in the collection of The Home for Aged and Infirm Hebrews, New York.)

pon to perform an autopsy on Thomas Parr, "a poor countryman . . . having lived one hundred and fifty-two years and nine months and survived nine princes." Parr had been brought up to London by the Earl of Shropshire to be exhibited to the King as a prodigy of longevity. Harvey's own account (7) of his findings is a revealing picture of the medical reasoning of that day. Death is ascribed to change of climate and to the richness of the London diet.

*"Whence the stomach at length failing, and the excretions long retained, the work of concoction proceeding languidly, the liver getting loaded, the blood stagnating in the veins, the spirit frozen, the heart, the source of life, oppressed, the lungs infarcted, and made impervious to the ambient air, the general habit rendered more compact, so that it could no longer exhale or perspire—no wonder that the soul, little content with such a prison, took its flight."*

Death actually seems to have been caused by pneumonia, but for all the details the whole protocol is worth reading. There is nothing in Harvey's words to indicate that he questioned the age of his subject (8). The centenarian has always fascinated both the layman and the physician, since he represents the attainment of the ultimate in longevity, and suggests that if his secret could be but fathomed, like success might be achieved by others. Since the time of Harvey a considerable literature has accumulated devoted to post-mortems of individuals 100 years and over (9).

Another famous medical experimenter and originator was Sanctorius (1561-1636) of Padua, who invented a clinical thermometer and a pulse-clock, as well as many surgical instruments. His *Ars de statica medicina* has been considered the earliest effort toward an experimental approach to the problems of metabolism, since his most celebrated accomplishment was the quantitative proof of the insensible perspiration. According to Stendel (10), old age to Sanctorius was an increasing difficulty in the insensible perspiration which finally led to suffocation and death. The frontispiece to the book shows the author seated in a chair suspended from a scale whereby he can weigh himself before and after eating. In this book occur several aphorisms on old age (11).

*"There is a great deal more perspired in youth than in old age; and the quantity of perspiration differs according to different constitutions, ways of living, climates and seasons."*

*"If you know what quantity of food you ought to take daily, and can adjust your exercise to it, you know how to preserve your health to old age."*

*"Violent exercise of body and mind persisted in brings on an early old age, and a premature death."*

*"Old men are destroyed by indulgences (sexual) of this kind, which render them heavier, weaker and colder."*

Revolutionary as were the techniques of Sanctorius in applying quantitative methods to medical problems, he had been anticipated a century and a half earlier by Nicholas Cusanus (1401-1464), Cardinal and Bishop of Brixen (12). This brilliant thinker in his *De staticis experimentis*, published in 1450, proposed to weigh the urine and blood and to evaluate the pulse rate by weighing the amount of water collected from a dropper-device while counting a standard number of beats. He believed that these methods would show marked differences in health and disease, in youth and in old age, and further, would have practical value.



rather gain, which I have never regretted and about which I twitted Dr. Rudisch many a time until, eventually, it became a bond of friendship between us.

I could reminisce indefinitely about the good old times in the shabby, wooden floored hospital at 67th Street, with its informality, pressure of work, understaffed interns, earnest, progressive attendings, competent nurses, and the then hardly known laboratory aids in default of which the six senses (common sense, the sixth) had to substitute, were it not my main task to describe the growth and development of gynecology and of the gynecological service.

The Mount Sinai Gynecological Service was organized in 1877. Its first head was Dr. Emil Noeggerath, famous for having recognized latent gonorrhea in women (1876) and co-founder with Abraham Jacobi of the American Journal of Obstetrics in 1868. To me he remains a mythical personage. He resigned from the hospital in 1882 and returned to Germany in 1895 where he died shortly thereafter. His incumbency at The Mount Sinai Hospital was of short duration. His activities, doubtless, were limited to the "office" and minor gynecology current in those days. Only few and bold spirits during this era ventured to invade the abdominal cavity to remove ovarian growths.

His successor was the handsome, dramatic and colorful Paul F. Mundé who reigned undisputedly from 1883 to 1902, until the day of his death from heart disease. He had run the gynecological class in the dispensary from the time of its foundation in 1875.

The career of Paul Fortunatus Mundé was sufficiently variegated to deserve recounting. His father, a physician in Dresden, fled to the United States after the revolution of 1848-9. Paul was educated at the Boston Latin School, entered the Yale Medical School, which he left to become an acting medical cadet in the Union Army in 1864. He completed his studies at the Harvard Medical School. The next seven years were spent in Europe. His postgraduate medical studies were again interrupted by two wars. In 1866 he helped fight the Prussians as assistant surgeon in the Bavarian Army. In 1870 he was battalion surgeon in the Bavarian Army. At the siege of Paris his hospital went up in flames, and he displayed great bravery for rushing through the fire and carrying out two wounded men who had been given up as lost.

In 1871 he received the degree of Master of Obstetrics in Vienna. He visited Paris, London and Edinburgh and in 1873, settled in New York. He performed his first laparotomy (ovariotomy) in 1877. He was a member of the New York Obstetric Society at a time when Sims, Peaslee, Emmet and Gaillard Thomas were still active, and a Founder Member of the American Gynecological Society. He functioned as Professor of Gynecology both at the New York Polyclinic and the Dartmouth Medical School.

As extern I was assigned to the gynecological ward and got to know the then ailing and aging Dr. Mundé very well. He was overweight, plethoric and short of breath but still showed charm and the remnants of virile good looks. He alternated between choler and geniality from day to day; it was hard to guess what his mood would prove to be. If he sat down on the examining room stool and told somewhat off-colored anecdotes, which made all the nurses—except the

supervisor—blush, it meant that the day was to be sunny and pleasant. If on the other hand he gloomed, each elevation of temperature was ascribed to the carelessness of the unlucky “ward-man”—myself.

Mundé left an extensive record of his work from 1883–1894 in an article appearing in the *American Journal of Obstetrics*, 1895. This report may be regarded as a fair resumé of the state of gynecology before 1900 and is worthy of careful reading.

In this eleven year period, the yearly number of admissions rose from 181 in 1883, to 505 in 1894. During the summer months other attending surgeons substituted for Mundé—Scharlau, Wyeth, Fluhrer or Gerster. After 1895, Joseph Brettauer, as adjunct gynecologist, took the summer service but was not welcomed to the ward at other times.

The twenty bed ward was 75 feet long, 24 feet wide, with a 15 foot ceiling. In spite of eight large windows on each side which gave ample air and light, the general effect was drab and depressing. In back was an examining room; in front were two small (hall-bedroom sized) cubicles, the one reserved for what now corresponds to semi-private, the other the “laparotomy room” for the first week’s convalescence of celiotomies.

Mundé represented the direct transition from the earliest women’s surgeons such as Sims, Emmet, Hegar, Simon and Stolz to the more modern school fathered in this country by Howard Kelly, Noble, Pryor, Price, etc.

In his earlier days, plastic repair, curettage, drainage of abscesses, “conservative” treatment of fibroids (ergot, curettage, intrauterine galvanization, removal of polypi) and the rare celiotomy for ovarian growths covered gynecological activities. In his later years deep cauterization of cervical cancer, occasional vaginal hysterectomy for the same, an increasing number of abdominal hysterectomies for fibroids with ligature of the transfixed cervical stump, the rubber ligature brought out through the lower angle of the incision, were resorted to. Pus tubes were removed through small abdominal incisions, liberated blindly by the fingers. After being freed, the pus sacs popped out of the incision, either intact or ruptured. Extrauterine pregnancies were diagnosed and successfully treated (16 with 2 deaths). Postoperative convalescence of laparotomies was protracted and stormy, not infrequently complicated by intestinal obstruction or “peritoneal sepsis.”

Mundé showed critical judgment ahead of many of his contemporaries in not ascribing over-importance to cervical tears, relaxed vaginal walls, lacerated perineums, retroflexions, etc., to the effects of which, in those days, the profession at large ascribed innumerable symptoms. Nevertheless, correction of these conditions played a major role on the gynecological service. He recognized that the then current operation for repair of cystocele (Stolz’s tobacco pouch circular suture) rarely lead to permanent cure, but had developed no improvement in technic. Silver wire was used to suture the cervix and to repair vesicovaginal fistulae (in Sim’s position).

To see Dr. Mundé operate was quite a spectacle. He donned a sleeveless undershirt and white linen trousers, “freshly baked *after* each operation.” Over

this a short rubber apron was tied and to complete the ceremony, after the hands and muscular, hairy forearms had been scrubbed and dipped in a weak bichloride solution, a fresh linen apron was draped over all. In the meanwhile the patient was strapped to the table, deeply anesthetized by means of an ether cone or by chloroform dripped on an open mask by an extern; scrubbed almost to the derma with soap and brush; laved with alcohol and then with ether. The operative area was draped sketchily with towels rung out in bichloride; a small median incision rapidly made. Then the operator, depending on the condition, inserted two fingers, or the whole hand, into the incision, half turned his back to the table and worked rapidly by touch alone, while the two assistants stood tensely alert. The climax was heralded by a few convulsive movements of the arm, than out popped a pus tube or hydrosalpinx, the pedicle of which was secured by the "Staford shire knot." The incision was closed by through and through sutures.

The uterus in every case of incomplete abortion was explored with the finger, scraped with a dull curet and lavishly irrigated with lysol solution. Pelvic cellulitis and subsequent pelvic abscesses were numerous; serious or fatal puerperal sepsis and peritonitis were of frequent occurrence; incision and drainage for abscess was performed in the ward examining room with or without anesthesia, depending upon the depth of its location and the fortitude of the patient.

By 1900 the old hospital had become antiquated. The wards frequently were overcrowded; emergency rows of beds, on occasion, cluttered the center of the wards, interfering with circulation, obstructing ward activities, and destroying all privacy. The house staff accommodations were uncomfortable and insufficient, their dining room tiny and ill ventilated.

The laboratory, as repeatedly mentioned in other retrospects which have been published, was minute, ill-equipped and inadequate. The sole means of sterilizing media consisted of a felt covered Arnold sterilizer. As junior intern, assigned to the laboratory service, one day I was called away for an emergency and I left the gas burner on. The Arnold sterilizer boiled dry, the smouldering felt-covering belched forth columns of smoke and stench. Firemen from the company across the street entered by means of a ladder, turned off the gas and ripped off the felt cover. I was fined \$10.00 to make good the damage, narrowly escaping court martial. In spite of these deficiencies, the work performed in the laboratory, due to enthusiasm, and good quality, yielded satisfactory results.

The whole hospital consisted of one close knit family which shared its joys, sorrows, and vicissitudes.

The externs (one year appointees) theoretically "slept out" but after assisting at operations until long after midnight, frequently bunked in with some friendly intern. One of their most despised drudgeries consisted of the biweekly routine examination of urines, which tempted one on occasions, to do the famous "*Sink Test*"—pouring the urine into the hopper and reporting "Negative" for albumin, sugar and other constituents. A summer substitute on the house staff, whose reports invariably read "five million red blood cells", was detected in making his red blood cell counts by the simple formula of counting one cell and multiplying by five million.

At this time one of the externs of outstanding personality, heard, by the grapevine route, that the superintendency of the hospital would shortly become vacant. To our surprise, he bearded the Board of Directors (now known as Trustees) and, according to rumor, was flatly turned down by that august body. However, he persevered, eventually wore their resistance down, thus launching upon a widely known and illustrious career which culminated in being appointed as Commissioner of Health and finally as Commissioner of Hospitals of New York City. The late S. S. Goldwater was the man to whom I refer; he became one of the best known hospital architects and hospital consultants in this and other countries.

In 1903 the new Mount Sinai Hospital at 100th Street and 5th Avenue neared completion. At the time it was the largest and most modern structure of its kind in the city. The capacity of the gynecological ward was doubled and the service split between Drs. Joseph Brettauer and Florian Krug, appointed as successors to Mundé. At the same time, adjunct gynecologists were chosen—Hiram N. Vineberg and Samuel M. Brickner. The complete change into modern surroundings, as well as the change in personnel, coincided with and marked the dawning of a new era in gynecology. By this time aseptic technic was ingrained and practiced as a matter of course by the younger group. Celiotomy now could be performed with impunity. Extensive—not infrequently *too* extensive—operations were resorted to. For example on the same patient the Edebohls procedure of nephropexy, appendectomy, ventrofixation and complete vaginal plastic at one session was current in some institutions. Mechanistic concepts ruled throughout surgery as evidenced in gynecology, by the innumerable operations devised for the correction of uterine retroflexion (over 100 methods and modifications according to Crossen). “Opening” of the cervix for sterility by dilatation, stem-pessary, Dudley, or Pozzi operations were performed daily. The results then obtained are equalled only by the marvels now ascribed to “endocrine therapy,” for all of which miracles old Mother Nature eventually may receive at least a modicum of credit.

The transition between the office-medical gynecology represented by Noeggerth, was bridged by Mundé, who advanced with the times and eventually developed into a dexterous abdominal surgeon. However, both he and his contemporaries never quite overcame the handicaps resulting from their ingrained fear of invading the peritoneal cavity, lack of adequate exposure, imperfect asepsis, insistence on voluminous drainage, and irrigation of intraperitoneal pus foci.

Personally, I took no part in the transfer and settling down process which accompanied the move from 67th Street to 100th Street. I spent four months as resident at Sloan Maternity Hospital, then at 59th Street and Amsterdam Avenue, which Edwin Cragin ruled autocratically but efficiently. An autodidact of limited vision, he was nevertheless endowed with executive ability, tremendous energy, manual dexterity and devotion to his task. The routine was iron clad, effective though narrow.

Subsequently eight months in Europe showed me that then already our surgery compared more than favorably with that practiced on the continent. Famous old holdovers such as the general surgeon Von Bergmann and the gyn-

ecologist Von Ohlshausen in Berlin were far behind the times. The next generation was still subordinate and suppressed in minor positions.

However, in internal medicine, pathology and in some of the specialties, the postgraduate student found wonderful facilities for increasing his knowledge due to the fact that human material could be herded and readily was available; that opportunities and facilities were purchasable on a strictly commercial basis in well organized classes and groups which varied from the general, designed for "*hoi polloi*" to the *privatissime* reserved for the few and privileged.

A few shining exceptions deserve mention. Professor Ludwig Pick, the pathologist, short, rotund, smiling and bald, who prided himself on his English which was a mixture acquired from his American pupils, interlarded with slang derived from all parts of the U. S. A., gave courses in pathology. After two or three months, if you measured up to his standards, you were given literally the freedom of his laboratory and of his world famous collection, as well as his friendship and advice. From him you could obtain the "low down" about every teacher in Germany and Austria. Innumerable graduates of Mount Sinai hold him in loving regard.

Prof. Lazare gave a course in dermatology to which everyone was welcome. He held it in the "Circus," a large hall which was crowded. Of the auditors, some 6-8 took the course; the rest were "ringers," but these were treated far more cordially than the regular students whom he despised and characterized by the German equivalent of "bone-heads." The material was staggering in its abundance and variety. One day he asked what type of cases I would like to see at the next session. I suggested leprosy and yaws. Next week he showed us six lepers and two tropical yaws.

My appointment to the attending staff in 1906 as adjunct gynecologist on Dr. Krug's service gave me the opportunity of continuing my connection with Mount Sinai. The fifth floor of the surgical pavilion just as now, then housed the two services—those of Brettauer and Krug. A large O.P.D. service was situated in the dispensary building. The main improvement in equipment that has taken place in the past forty years consists in the installation of movable curtains about each bed, affording privacy; the roof garden on the adjacent roof of the neurological building, made accessible by building a bridge; installation of a lounge for patients, and the complete remodelling of the gynecological dispensary. This speaks well for the original planning.

The two gynecological services were entirely independent, headed by two men of different personality and training. The resulting rivalry was friendly, critical and of greatest value to the house staff who had the opportunity of seeing and comparing different points of view and different methods.

Dr. Florian Krug (1838-1924) was a newcomer to The Mount Sinai Hospital. At the time of his appointment in 1904 he was forty-five years of age. He was born in Mainz, received his degree of M.D. in Freiburg in 1882, continued his studies as an assistant to Hegar, completing them in Vienna and Paris. In 1885 he settled in New York and in 1888 became attending gynecologist to the German Hospital (1888-1907—now the Lenox Hill Hospital).



Dr. Krug had the advantage of being trained by Hegar, one of the pioneers in gynecological abdominal surgery. He early recognized the value of the Trendelenberg position; operated with full exposure, dexterity and boldness; performed hysterectomy with smoothness and success before the technic had been perfected throughout the country.

Personally he was a man with charm, endowed with good looks, a famous *raconteur* and *bon-vivant*. On the other hand he rarely contributed to medical literature but did some teaching as Professor of Gynecology at the New York Polyclinic. He ran his service with conscientiousness and success, but, as far as I can judge, otherwise took no keen interest in the affairs of the hospital. Consequently his influence and instruction was limited to those who came into immediate contact with him. During the last few years of his incumbency, which ended by resignation in 1915, ill health placed much of the burden of conducting the work upon the shoulders of his successor, Dr. Hiram N. Vineberg.

The other gynecological service was headed by Joseph Brettauer who had worked in the out-patient department since 1893, and as summer adjunct since 1895. Brettauer, born in Austria (Hohenems, 1863) graduated in medicine at Gratz (1887) and received a thorough training in abdominal surgery with Wölfler, a pioneer in gastric operations. His training in gynecology and obstetrics was received in the clinics of Chrobak and Breisky. Dr. Brettauer came to New York in 1890 and functioned as attending gynecologist, without a break, between 1902 and 1925. During the last four years of his service, after the retirement of Dr. Vineberg, he controlled all the gynecological beds.

Brettauer was a powerful, athletic, energetic individual of dominant personality, endowed with drive and self reliance. He made friends readily and kept them throughout life. He inspired confidence and hopefulness in his many patients and was a popular consultant.

Perhaps partly due to the fact that his medical training was received when asepsis was already in full swing abroad, and because it included general surgery before he received his specialistic education, Brettauer's technic was completely modern from the outset and required little change or revision as time passed. He was a quick, bold, resourceful operator whose every motion was purposeful. Having had a thorough training in pathology, a mere glance sufficed to evaluate the situation, plan his mode of attack and execute it. Many visitors came to watch him operate. Brettauer contributed little to the literature, rarely explained what he was doing; his teaching was strictly personal and by example. His influence, however, was widespread and lasting. He treated inflammatory pelvic conditions on conservative lines at a time when operative intervention was practiced universally. On the other hand, his operations for abdominal growths—fibroids, ovarian tumors, carcinoma of the cervix were bold and radical. He was equally conversant with the abdominal and vaginal approach. His plastic surgery was based upon the anatomy and was a great advance over that practiced by Stolz, Hegar and others of the earlier group.

To the present generation many of our modern aids are so much a matter of

course that they do not realize how such aids as the Trendelenberg table, suction removal of pus or blood, transfusion of blood, rubber gloves, improvement in anesthesia, facilitate operative work and safeguard the patient.

The technics used throughout this period differ in few ways from those now used. Extraperitoneal shortening of the round ligaments or ventrofixation combined with anterior and posterior colporrhaphy was the routine operation of choice for prolapse of the uterus. By 1913 x-ray therapy for fibroids was begun and the indications and contraindications worked out. At the beginning, ten to fifteen patients were grouped radially, standing about one x-ray tube; treatment involved up to fifty sessions extending over several months. No filters were used; several severe x-ray burns developed. About this time, also, radium treatment of carcinoma of the cervix was tried out with 130 mg. of radium substance placed at my disposal by the Crocker Cancer Research Laboratory of Columbia University.

There never was a dull moment on Brettauer's service in all the years. Rain or shine he appeared on the Ward at the stroke of nine with all the staff. Each patient received at least a kindly word. All the new patients were waiting on wheeled stretchers or on chairs at the door of the examining room. Each of them, after the reading of the history, was examined in turn. Whenever possible, the associate and adjunct then examined the patient also, unless fear or pain contraindicated. Lively discussion followed, usually listened to patiently by the chief. Now and then, if one of us grew verbose or a bit pompous, a terse, deflating interjection burst the bubble of our complacency. Usually he was in the right because his clinical acumen and flair was uncanny, although he never sought for minutiae of diagnosis. There were few dressings to be done as little drainage was used and wounds healed by primary union. By 10 a.m. the ward was quiet for the day. However, strict supervision of the nursing, the serving of meals, and similar ward activities was maintained by unheralded visits by day and even by night.

Brettauer's unconventionality, disregard for form and rules, as well as eccentricities, which he could turn on or off at will, gave rise to many tales and anecdotes. He frequently, but only when asked, gave sage advice, although he himself did not follow these precepts invariably. I recall seeking him out one day when I was boiling with indignation because of an injustice. After listening to my tirade, he remarked, "When you're young, you must learn to swallow (by him pronounced "schwallow"), and swallow and swallow; by the time you're older, you have learned how to do it." He was known throughout the hospital as "Uncle Joe". His physical strength was colossal. Again and again I have seen him shoulder aside two husky orderlies who were struggling to transfer an overweight patient to the operating table. Unaided he would heave her up from the stretcher and carry her to the table. In 1925, Dr. Brettauer retired from the ward service because of the age limit (62 years for surgeons, 65 years for internists—presumably the latter are credited with slower senescence). He continued actively in private practice until the occurrence of a severe anginal attack in

1928. From then on he was obliged to curtail his activities more and more. Throughout he retained his interests, his contacts with friends and his cheerfulness. He died suddenly and peacefully in December of 1941.

No history of the gynecological service would be complete without mention of Dr. Samuel M. Brickner, associate from 1903 to 1913, whose scholarly poise, sweetness of character and literary talent endeared him to many. He was connected with the service for ten years. He resigned in 1913 because of continued illness and died at Saranac Lake in 1916 at the age of forty-nine. He was assistant editor of the New York Medical Journal and of the American Journal of Surgery, and Editor of the Medical Pickwick. Many of his poems were widely quoted. Shortly before his death he wrote his own valedictory:

#### THE FEAST<sup>1</sup>

DR. SAMUEL BRICKNER

There is no more Lucullan feast than this  
At which I daily sit;  
Laughter and sunshine, love, a tender kiss—  
These are the Sweets of it.  
If by chance, black stormclouds lowly bend  
My unresisting head,  
It is no symbol that my joy shall end,  
For still my feast is spread.  
A day will come, with laughter just as sweet,  
The sun will fill the air,  
Love still be young but other lips will meet;  
I shall have had my share.

During the years 1906 to 1907, upon my appointment to The Mount Sinai Hospital, I served as adjunct on Dr. Krug's service; thereafter (1907 to 1917) as adjunct and associate on Dr. Brettauer's. In addition to the routine, which involved a most thorough training in gynecological diagnosis, and treatment including operative technic, my spare time was occupied in research.

As the doors of the laboratory of Mount Sinai remained closed to me, I performed my work at the College of Physicians and Surgeons, in Dr. T. Mitchell Prudden's Department of Pathology, Dr. Gies's Department of Biochemistry and the Rockefeller Institute (Dr. Simon Flexner), as well as in Dr. Huntington's Department of Anatomy. This was before the days of the automobile, consequently involving many a midnight walk. I remember one night stepping into the automatic elevator on the ground floor in the old Physicians and Surgeons building, deserted and dark, only the elevator was not there, and I dropped down one flight into the basement where there was no exit door. Eventually, after recovering from the shock, I clambered out by balancing myself on the narrow central bumper and launching against the sill to which I clung and then chinned myself up—a feat of which I am no longer capable today.

I mention the researches because, eventually, they influenced the service to some extent. Endocrinology was in its infancy. The sole investigator in this

<sup>1</sup> Reprinted in the Saranac Lake News by the author's request, the day before he died.

country, then engaged with gynecological problems, was Leo Loeb whose outstanding contributions on the function of the corpus luteum are too well known to require elaboration. My work at first dealt with the endocrine function of the placenta and later branched out to include the corpus luteum and follicle of the ovary. In these investigations, which included attempts to obtain purified extracts, I was aided by enthusiastic volunteer assistants and collaborators—Dr. Abe Unger, one of our graduates, T. Lefkowitz, a brilliant and charming medical student who died in his Junior year, and Dr. Jacob Rosenbloom who died in Pittsburgh at an early age.

The placental work proved so promising, that Dr. Francis Carter Wood, upon the opening of the Crocker Cancer Research Laboratory, invited me to transfer my work there, and placed the facilities of the chemistry laboratory of St. Lukes Hospital at my disposal. Here a huge still was built, a still which permitted the extraction of 500 human placentae at one time. Daily the laboratory boy visited the various New York maternity hospitals, brought back the afterbirths, ground them up and placed them, submerged in alcohol, into huge earthen jars—currently called Ali Baba's in the laboratory. Under a grant I had the assistance of a chemist, Mr. O. I. Lee. Once and once only, while cracking pure cholesterol, we succeeded in obtaining an active estrogen, but we were unable to duplicate the experiment. Later Lee was succeeded by a graduate student in chemistry, Paul M. Giesy, who developed a method of separating the extracts between petroleum ether and alcohol, a fundamental method still in use.

Although the older school gynecologists regarded with the utmost scepticism the results obtained, Brettauer (himself unconvinced) encouraged me continuously and backed me up loyally in my fight with the earliest "clinical endocrinologists" (a term then as yet unborn) who cured patients as successfully then as now.

The other research was anatomical, undertaken at the outset purely for self-educational purposes. It involved dissection of the pelvic muscles, fasciae and connective tissues (aided by Dr. Samuel Geist, appointed adjunct gynecologist on Krug's service in 1913). I wangled an appropriate cadaver now and then at the anatomical laboratory of Dr. Huntington, which we then dissected, measured and photographed minutely, and from which I reconstructed models. This study eventually helped to place the repair of cystocele upon a sound, anatomical basis and secured a greater percentage of cures.

As an example of the peculiar tricks that fate can play, I shall mention one more personal incident. In May 1917, I discovered that the follicle fluid of cow's ovaries contains a concentrated form of estrogen. I incorporated these findings in a report prepared for, but never delivered at the American Gynecological Society which met on May 31st, 1917. Just as I was stepping into a cab to go to the station, I was handed a telegram calling me into military service. For me the meeting was off. Two years in the service and subsequent illness prevented me from publishing these results until January 1922. This incident, as far as I was concerned, has convinced me that General Sherman was fully justified in his famous dictum!

Upon the resignation of Dr. Krug in 1916, Dr. Hiram N. Vineberg was ap-

pointed attending on the Second Gynecological Service. Dr. Vineberg was born in Russia in 1857, transplanted to Canada during infancy and there received his education. He graduated in medicine at McGill University in 1878, where his training was mainly in medicine. In 1886 he moved to New York City and has remained here ever since. From 1890 he worked in the Gynecological O.P.D. He functioned as summer adjunct in the hospital from 1898 on and was appointed associate on Krug's service in 1904.

Dr. Vineberg, as so many surgeons and gynecologists of that day, was largely autodidact. Well do I remember the grim concentration, the indomitable persistence, and the slow, careful technic of his operations. He expended meticulous care and thought in studying the patients, was exact in diagnosis because he evaluated every symptom and physical sign. Few knew the medical literature as well as he did, and fewer could apply such knowledge with the exactitude that he did. It is not surprising, therefore, that he spotted chorio-epithelioma with comparative frequency, a disease which others overlooked. He developed the diagnosis of this treacherous disease and contributed to its proper treatment. Vineberg, as early as 1896, devised a method of shortening the round ligaments by vaginal section. I noticed recently that his operation of supravaginal hysterectomy by the vaginal route has been revived by TeLind and Richardson, as a novum. Most medical authors today content themselves with search of the literature for at most five years back—anything more antique is outlawed and forgotten—hence medical “nova” rival those of the firmament in number.

Vineberg took an active part in the discussion as to whether bleeding ectopic gestation should be operated upon at once or the patient “hibernated.” This question, which has long since become purely academic (since blood transfusion was introduced) was then debated with acrimony. I remember one patient brought in *in extremis*. Vineberg slashed her open; placed a clamp on the broad ligament almost by feel (before the days of suction); the anesthetist declared the patient dead—somewhat prematurely—, an adhesive strap across the wound with clamp *in situ*—the patient recovered.

The treatment of inflammatory tubal conditions was more radical on the Second Service than on the First Service. Both Krug and Vineberg operated upon tubes much earlier than Brettauer did. In my opinion the results of earlier intervention resulted in some increase in mortality and in marked frequency of stormy convalescences, suppurating wounds and frequency of drainage. On the other hand, Vineberg recognized rupture of pyosalpinx into the free peritoneal cavity and salvaged these patients. This moot question, today also may be relegated into the archives, particularly since the sulfa drugs have placed a potent weapon against the gonococcus and streptococcus in our hands.

Dr. Vineberg retired from the ward service because of the age limit in 1921. He continued his private practice for a number of years. He died after a short illness, in May of this year at the age of 88 years. Surviving contemporaries, friends and pupils, have joined in tribute to him and published in 1943, a special number of the Journal of The Mount Sinai Hospital as an “Anniversary Volume” in his honor.



During Dr. Vineberg's regime on the Second Gynecological Service, one of his adjuncts, Dr. I. C. Rubin, made a major contribution to gynecology—his method of tubal insufflation with gas—at first with air, later with carbon dioxide. This method, as well as studies which have developed therefrom, have completely revolutionized the diagnosis and treatment of sterility and have enabled the profession to recognize with certitude sterility due to mechanical obstruction.

When the time for Dr. Brettauer's retirement approached in 1925, I, then resident and practicing in Denver, Colorado, was invited to succeed him, an invitation which I accepted with pleasure. My enforced separation from the hospital between 1917 to 1925 had in no way diminished my interest and close relation with the institution which I have regarded always as my *Alma Mater*.

However, I have no intention of inflicting the reader with an account of my incumbency which covered the years 1925-1937, but will leave this to another recorder should the occasion arise. I returned to find a model gynecological service of 40 beds, fully staffed and in fine running order.

Gynecology, at this time, was again undergoing the pains of parturition. The era of "dead" pathology and mechanistic concepts was declining. Physiology, physics, chemistry and endocrinology were exerting activating influences which tinged investigations, diagnosis and therapy. Psychology and psychosomatic studies helped to weed out patients whose complaints had resulted in pelvic "fixations"—patients who previously had been subjected to operation without relief. Birth control, almost surreptitiously, was whispered about in medical circles. The first clinic of this kind in any hospital in this country, was established in The Mount Sinai O.P.D. in 1925, and was headed by the late Dr. Max D. Mayer.

Today, after the elapse of less than two decades, our knowledge of the potency of the vitamins and of the marvellous effects of chemotherapy mark another milestone. Looking backward over more than 40 years, the general "speed up" which the laity envision in terms of the automobile and the aeroplane, which have abolished distance, has affected medicine concordantly. The advances in medicine, in retrospect, are proportionately rapid, marvelous and equally promising for the future.

LIFE'S LATER YEARS  
STUDIES IN THE MEDICAL HISTORY OF OLD AGE

FREDERIC D. ZEMAN, M.D.

[New York City]

PART 9<sup>1</sup>

THE SEVENTEENTH CENTURY

*"For we have hope, and wish, that it may conduce to a common good, and that the nobler sort of physicians will advance their thoughts, and not employ their time wholly in the sordidness of cures, neither be honoured for necessity only; but that they will become co-adjutors and instruments of the Divine Omnipotence and Clemency, in prolonging and renewing the life of man; especially, seeing we prescribe it to be done by safe and convenient and civil ways, though hitherto unassayed."*

*Francis Bacon—Foreword to the  
History of Life and Death.*

Against a background of epoch-making achievements in art, literature, music, philosophy, mathematics and natural sciences, we find medicine striking an accelerated pace that has but rarely slackened in three hundred and fifty years. In the seventeenth century we behold the first fruits of the great intellectual emancipation that came with the overthrow of tradition and the application of what we now call the scientific method, the reasoned combining of observation, correlation and experimentation.

As a symbol of the transition between the old and new thinking, Shakespeare (1564-1616) stands preeminent as uniting with his great poetic gift a thorough grasp of the general knowledge of his time. It was given to him to cover the whole range of human experience with understanding such as no one had ever before possessed; but his imagery is all in terms of what had been learned and taught by the men who came before him (1). His physiological concepts of old age are apparent in these lines, based on the time-honored teachings of Galen that the quantity of blood in the body diminishes with advancing age, and that in characterizing old age as cold and dry, all its manifestations are explained.

*"Yet who would have thought the old man  
To have had so much blood in him?"*

*Macbeth—Act 1, Scene V.*

<sup>1</sup> This is the ninth in a series of articles dealing with Studies in the Medical History of Old Age. Upon completion of their publication, the installments will be collected and reprinted in a single volume, constituting the third in the Series of Monographs of The Mount Sinai Hospital Press.—Ed.

*"Though now this grained face of mine be hid  
In sap-consuming winter's snow,  
And all the conduits of my life froze up,  
Yet hath my night of life some memory."*

*Comedy of Errors—Act V, Scene 1.*

*"These old fellows  
Have their ingratitude in them hereditary:  
Their blood is caked, 'tis cold, it seldom flows.  
'Tis lack of kindly warmth they are not kind;  
And nature as it grows again toward earth,  
Is fashioned for the journey, dull and heavy."*

*Timon of Athens—Act II, Scene II.*

The roster of old men in the histories, the tragedies and comedies includes such well known figures as Lear, Prospero, Polonius and Falstaff, and several lesser ones, such as Aegeon, Nestor, Belarius, Capulet and Adam. The play *King Lear*, has been called by John Masefield the most affecting and grandest of Shakespeare's creations. For the present theme it not only furnishes the unequalled picture of senile deterioration aggravated by overwhelming misfortune, but also illustrates the conflict of parent and children in two separate examples, the old king and his three daughters, contrasted with Gloucester and his two sons, the legitimate but evil Edgar and the dutiful, unselfish bastard, Edmund.

His appraisal of life is to be found in the famous speech of Jacques, in which we recognize the familiar sad echoes of Ecclesiastes, Aristotle, Horace, Juvenal and Chaucer.

*"All the world's a stage,  
And all the men and women merely players.  
They have their exits and their entrances;  
And one man in his time plays many parts;  
His acts being seven ages. At first the infant,  
Mewling and puking in the nurse's arms.  
And then the whining school-boy, with his satchel  
And shining morning face, creeping like a snail  
Unwillingly to school. And then the lover,  
Sighing like a furnace, with a woeful ballad  
Made to his mistress' eyebrow. Then a soldier,  
Full of strange oaths, and bearded like the pard;  
Jealous in honour, sudden and quick in quarrel,  
Seeking the bubble reputation  
Even in the cannon's mouth. And then the justice,  
In fair round belly with good capon lined,  
With eyes severe and beard of formal cut,  
Full of wise saws and modern instances;*

*And so he plays his part. The sixth age shifts  
 Into the lean and slipper'd pantaloon,  
 With spectacles on nose and pouch on side;  
 His youthful hose, well saved, a world too wide  
 For his shrunk shank; and his big manly voice  
 Turning again toward childish treble, pipes  
 And whistles in his sound. Last scene of all,  
 That ends this strange eventful history,  
 Is second childishness, and mere oblivion,  
 Sans teeth, sans eyes, sans taste, sans everything."*

*As You Like It—Act II, Scene VII.*

From the greatest of English poets, we turn to one whose intellectual gifts are so impressive that some have even ascribed to his hand the whole of Shakespeare's endeavors. Francis Bacon, Baron St. Albans, Lord Verulam (1561-1621) presents from the standpoint of character one of the great enigmas of history, since in him we find both the philosopher's search for truth and a ruthless political opportunism. The poet, Alexander Pope, called him "the wisest, brightest, meanest of mankind." His influence on his contemporaries and on the following generations was due, not to his own original contributions which were negligible, but to his unremitting fight against authority, against uncontrolled flights of imagination and against wordy academic argument, all lucidly and forcibly expressed. His fundamental principles form the basis of modern scientific methods.

Among the many questions touched upon by Bacon in the wide range of his writings, the problem of old age, its nature and evaluation, is discussed at length. In the "Essays", reminiscent of Montaigne, and noted for their shrewd understanding and unusually vivid style, we find *Of Youth and Age*, a clearly drawn and well considered series of parallels, illustrating the salient mental characteristics of both periods of life.

*"Young men are fitter to invent than to judge; fitter for execution than for counsel; and fitter for new projects than for settled business. For the experience of age, in things that fall within the compass of it, directeth them; but in new things, abuseth them. The errors of young men are the ruin of business; but the errors of aged men amount but to this, that more might have been done or sooner. . . . Men of age object too much, consult too long, adventure too little, repent too soon, and seldom drive business home to the full period, but content themselves with a mediocrity of success." (2).*

In the *History of Life and Death* (3) Bacon's aim is far more ambitious, seeking among other things, as the epigraph to this chapter indicates, to educate "the nobler set of physicians." He scoffs at "these things which the vulgar physicians talk of, radical moisture and natural heat, (which) are but mere fictions; and the immoderate praises of chemical medicines first puff up with vain hopes, and then

fail their admirers." He differentiates death resulting from disease, and "death which comes by total decay of the body, and the inconcoction of old age." He ascribes old age to failure of the power of reparation of the tissues.

*"There is, in the declining of age, an unequal reparation; some parts are repaired easily, others with difficulty, and to their loss; as, from that time, the bodies of men begin to endure the torment of Mezentius; that the*



FIG. 1. Francis Bacon, Baron St. Albans, Lord Verulam (1561–1621), "The wisest, brightest, meanest of mankind." (Reproduced from print in the collection of The Home for Aged and Infirm Hebrews, New York.)

*living die in the embrace of the dead; and the parts easily reparable, through their conjunction with the parts hardly reparable, do decay . . . and that the cause of the termination of life is this; for that the spirits, like a gentle flame continually preying upon bodies, conspiring with the outward air, which is ever sucking and drying of them, do, in time, destroy the whole fabric of the body, as also the particular engines and organs thereof, and*



*make them unable for the work of reparation. These are the true ways of natural death, well and faithfully to be revolved in our minds; for he that knows not the ways of nature, how can he succour her, or turn her about?"*  
(3)

The author discusses longevity in relation to heredity, the physical attributes of the long-lived, rejecting astrology, and dwells at length on the subject of diet, endorsing Cornaro, but pointing out that some liberal eaters also live long. As in the *Essays*, he compares youth and age mentally, but also goes into great detail regarding the physical features. In general Bacon's observations are sound, as he seeks to disprove the time-honored explanations of the phenomena of youth and age.

At this point Sir Thomas Browne (1605-1682), the famed physician of Norwich, who endeavors in *Religio Medici* to reconcile faith and scepticism, must be included in our narrative, not so much as a significant example of contemporary thought, but for his own peculiar merits (4).

*"But age doth not rectify, but incurvate our natures, turning bad dispositions into worser habits, and (like diseases) brings on incurable vices; for every day as we grow weaker in age, we grow stronger in sin, and the number of our days doth but make our sins innumerable. . . . I find my growing Judgment daily instruct me how to be better but my intamed affections and confirmed vitiosity make me daily do worse."*

To make our record more complete and to remind readers that Galen still ruled medical thinking on old age, in spite of the efforts of original minds, we must here mention several unimportant works by physicians of this period. Rodericus a Fonseca, professor at Pisa and Padua, published in 1602 a treatise entitled *De tuenda valetudine et producenda vita, ad Ferdinandum Medicem magnum Hetruriae ducem*, based frankly on Galen. Aurelius Anselmus of Mantua, physician to the Duke of Mantua, in 1606, wrote *Gerocomice sive de senum regimine*, praising the old for excelling in prudence and understanding. Franciscus Ranchinus, professor at Montpellier, was the author of *Gerocomice de senum conservatione et senilium morborum curatione*, in the year 1625. Rodolphus Goelemius, a German physician, dedicated his efforts, entitled briefly *De vita proroganda*, to Frederic, Count of the Rhenish Palatinate, and to Otho, Landgrave of Hesse, in 1608. Claudius Diodatus, physician to the Bishop of Basle, is responsible for a bombastic effort, given to the world in 1628, and based on "the vain boasts of the chymists", *Pantheon Hygiasticon Hippocraticum Hermeticum de hominis vita ad centum et viginti annos salubriter producenda* (5). One conclusion seems clear: the good will of people in high places, then as always, was sought after by physicians through the medium of well aimed dedications. In addition, Stendel tells us, old age was a favorite theme for medical dissertations and speeches at academic celebrations. In 1664, Heinrich Meibom, the famous anatomist of Helmstedt, delivered his *Epistola de longaevis* as a birthday talk for the *Landherr* (6).

The significance, both immediate and remote, of the publication of William Harvey's (1578-1657) *De Motu Cordis* in 1628, needs no further enlargement here. The distinguished founder of modern physiology, whose discovery forms the cornerstone of all medical thinking, comes into our studies in an entirely different rôle, that of pathologist. On November 14, 1635, Harvey was called



*The Olde, Old, very Olde Man or Thomas Parr, the  
Sonne of John Parr of Winnington in the Parish of Alcebury  
In the County of Shropshire who was Borne in 1483 in  
The Reigne of King Edward the 4<sup>th</sup> and is now living in  
The Strand, being aged 152 yeares and odd Monethes 1635  
He dyed November the 15<sup>th</sup> And is now buried in Westminster.*

FIG. 2. Thomas Parr (1483-1635), most famous of the supercentenarians. (Reproduced from print in the collection of The Home for Aged and Infirm Hebrews, New York.)

upon to perform an autopsy on Thomas Parr, "a poor countryman . . . having lived one hundred and fifty-two years and nine months and survived nine princes." Parr had been brought up to London by the Earl of Shropshire to be exhibited to the King as a prodigy of longevity. Harvey's own account (7) of his findings is a revealing picture of the medical reasoning of that day. Death is ascribed to change of climate and to the richness of the London diet.



*"Whence the stomach at length failing, and the excretions long retained, the work of concoction proceeding languidly, the liver getting loaded, the blood stagnating in the veins, the spirit frozen, the heart, the source of life, oppressed, the lungs infarcted, and made impervious to the ambient air, the general habit rendered more compact, so that it could no longer exhale or perspire—no wonder that the soul, little content with such a prison, took its flight."*

Death actually seems to have been caused by pneumonia, but for all the details the whole protocol is worth reading. There is nothing in Harvey's words to indicate that he questioned the age of his subject (8). The centenarian has always fascinated both the layman and the physician, since he represents the attainment of the ultimate in longevity, and suggests that if his secret could be but fathomed, like success might be achieved by others. Since the time of Harvey a considerable literature has accumulated devoted to post-mortems of individuals 100 years and over (9).

Another famous medical experimenter and originator was Sanctorius (1561-1636) of Padua, who invented a clinical thermometer and a pulse-clock, as well as many surgical instruments. His *Ars de statica medicina* has been considered the earliest effort toward an experimental approach to the problems of metabolism, since his most celebrated accomplishment was the quantitative proof of the insensible perspiration. According to Stendel (10), old age to Sanctorius was an increasing difficulty in the insensible perspiration which finally led to suffocation and death. The frontispiece to the book shows the author seated in a chair suspended from a scale whereby he can weigh himself before and after eating. In this book occur several aphorisms on old age (11).

*"There is a great deal more perspired in youth than in old age; and the quantity of perspiration differs according to different constitutions, ways of living, climates and seasons."*

*"If you know what quantity of food you ought to take daily, and can adjust your exercise to it, you know how to preserve your health to old age."*

*"Violent exercise of body and mind persisted in brings on an early old age, and a premature death."*

*"Old men are destroyed by indulgences (sexual) of this kind, which render them heavier, weaker and colder."*

Revolutionary as were the techniques of Sanctorius in applying quantitative methods to medical problems, he had been anticipated a century and a half earlier by Nicholas Cusanus (1401-1464), Cardinal and Bishop of Brixen (12). This brilliant thinker in his *De staticis experimentis*, published in 1450, proposed to weigh the urine and blood and to evaluate the pulse rate by weighing the amount of water collected from a dropper-device while counting a standard number of beats. He believed that these methods would show marked differences in health and disease, in youth and in old age, and further, would have practical value.

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On an entirely different level of medical endeavor, one that the eminent Lord Verulam would no doubt have found "less noble", we encounter Tobias Venner (1577-1660), "Doctor of Physicke at Bathe in the Spring and Fall, and at other times in the Borough of North-Petherton neere to the ancient Haven-towne of Bridgewater in Somersetshire." Thus reads his address on the title



FIG. 3. Tobias Venner (1577-1660). This portrait at the age of 85 years indicates a state of well-being rivaling that of Cornaro whose regimen did not include whiskey. (Reproduced from print in the collection of The Home for Aged and Infirm Hebrews, New York.)

page of his curious work, *Via Recta ad Vitam Longam* (13), justly renowned for his ardent advocacy of whiskey for old age and other ills.

"Now to the question I answer that for the most part there is not any water in use, which can better fortifie life and hinder the coming on of old age, than the aforesayd Aqua vitae; for it greatly comforteth a weak stomach, expelleth winde, putteth off all melancholike passions, preserveth the humours from corruption and excellently prevaiileth against swounding; 'or by reason of a notable penetrable power that it hath, it quickly goeth to the heart and wonderfully raiseth up faint and feeble spirits. But the use thereof is not alike wholesome and good for all bodies, for unto them that are leane, and of a dry nature, and in the Summer it is very pernicious be-

*cause it drieth up and (as it were) scorseth their inward parts, especially the liver and destroyeth the naturall moisture, but to old men, to grosse and moist bodies, it is very profitable, for it fortifieth their stomacks, concocteth excrement and all humours, discuteth winde, and defendeth them from the lethargie, apoplexie and other cold diseases unto which by reason of their moist habit of body, they are very subject."*

In an effort to limit the scope of this study we pass over the great achievements of the medical microscopists, Van Leevenhoeck (1632-1723), Malpighi (1628-1694) and De Graaf (1646-1673), to call to attention the beginning of vital statistics in England in the work of John Graunt (1620-1674), on the *Naturall and Political Observations upon the Bills of Mortality* (London, 1662), of Sir William Petty (1623-1689) who took the first census of Ireland and wrote *Essays on Political Arithmetic* (1687), and of the astronomer, Edmund Halley (1656-1742) who compiled the Breslau Table of births and funerals (1693). From these pioneer efforts gradually arose the great statistical studies furthered by governmental and private agencies that carry such weight in modern studies of life and death, as exemplified in the work of the late Raymond Pearl and in the publications of Dr. Louis Dublin.

In the field of clinical medicine we have such leaders as Thomas Sydenham (1624-1689), abnormally individualistic in his attitude to his medical predecessors and his colleagues but likewise abnormally gifted in the observation and differentiation of disease. In both his work on gout and on fevers he refers to the peculiar reactions of the old.

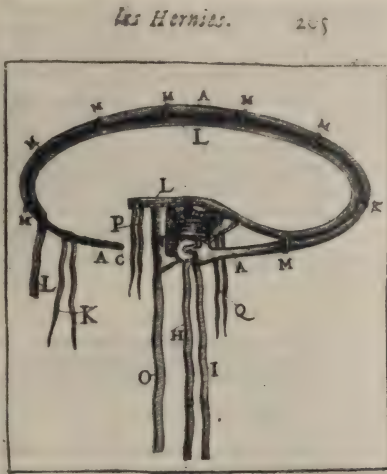
*"But in aged persons, affected either with autumnal tertians or quartans, there is danger of these diseases becoming not only obstinate but mortal; for which reason, if the bark and every other method prove ineffectual to a cure, nature must at least be supplied with such helps, as may enable her to finish her work."*

*"In many persons the gout breeds the stone in the kidneys. It seldom attacks women, and only the aged of this sex, and those of a masculine habit of body. Children and young persons rarely have it." (14).*

Thomas Willis (1621-1675) made significant contributions to the anatomy of the central nervous system, first describing the eleventh cranial nerve, to which his name is sometimes given, and pointing out the grouping of the arteries at the base of the brain which has ever since been known eponymically. Of all his notable achievements the most practical and important was the discovery that diabetic urine has a sweet taste, thus laying the foundation for the study of one of the most important diseases afflicting mankind and especially prevalent in the later years.

In this connection, it should be noted that Frederick Dekkers of Leyden in 1694 first detected albumin in urine in the presence of acetic acid. In pathology the work of Raymond Vieussens (1641-1716) of Montpellier in describing the course of the coronary arteries and the clinical picture as well as the pathology

of mitral stenosis and aortic insufficiency, is outstanding. It is to be correlated with the work of Sylvius (1614-1672) on the nature of phthisis and of Lancisi (1654-1720) on the rôle of the heart in sudden death. Wepfer (1620-1695) of Schaffhausen in 1658 described the hemorrhagic brain lesion of apoplexy.



**EXPLICATION DE LA**  
*Figure du Brayer à ressort*  
*inventé par l'Auteur.*

**A A A. La Ceinture du**  
**Corps du Brayer recouvert**  
**de cuir de mouton.**

FIG. 4. The Elastic Truss of Nicolas de Blegny (reproduced from his *L'Art de Guérir les Hernies*, Paris, 1676, by courtesy of the Army Medical Library, Cleveland Branch.)

As for the medical specialties, mention must be made of the advancement of the physical theory of vision by Kepler the astronomer and Descartes the philosopher; by Marriotte (d. 1684) discoverer of the blind spot, and by the Jesuit astronomer Scheiner (d. 1650) who "illustrated accommodation and refraction by the pinhole test which bears his name" (15). The first book on dentistry in English was published by Charles Allen in 1686. Nicolas de Blegny (1652-

1722) invented the elastic truss, described in his treatise on hernia (1676). All of these advances have had particular meaning for those who have "so long marched hand in hand with time."

In reviewing the high lights of this highly productive period much has necessarily been omitted entirely and theoretical controversies have not been touched upon since they have not seemed germane to our theme. Many of the discoveries noted were of importance for the future of medicine and indicate the earliest observation of phenomena that only to-day are beginning to be understood. Garrison has drawn a vivid, fascinating picture of the cultural and social background of this period (16). As to the actual treatment of the old it seems likely that, in view of prevalent faith in magical remedies, such as the weapon-salve and Digby's "sympathetic powder", in astrology, in animal magnetism and in strange remedies of all descriptions, the aged fared badly whether they treated themselves or consulted physicians. The prevalence and frequency of blood-letting and the wide variety of conditions for which it was prescribed, make it evident that Dr. Sangrado of Le Sage's *Gil Blas* typified a large part of the profession in putting every possible obstacle in the way of the patient's recovery.

#### REFERENCES

1. For interesting comments on the medical aspects of Shakespeare, see:
  - (a) ROBIN, P. A.: *The Old Physiology in English Literature*, London, 1911.
  - (b) SIMS, R. E.: *The Green Old Age of Falstaff*. *Bull. Hist. Med.*, 13: 157, 1943.
2. BACON, E.: *Essays, and Colours of Good and Evil*, W. A. Wright, London, Macmillan & Co., 1883.
3. BACON, F.: *History naturall and experimentall of Life and Death, or of the prolongation of life*, London: for W. Lee and H. Mosely, 1650. This is an English translation of the Latin version, made under the direction of Dr. Rawley who wrote a life of Bacon.
4. BROWNE, SIR THOMAS: *Religio Medici*, London, 1642.
5. MACKENZIE, J.: *History of Health*, Edinburgh, Gordon, 1758.
6. STENDEL, J.: *Zur Geschichte der Lehre der Greisenkrankheiten*, *Sudhoff's Archiv. f. Geschichte d. Med. u. d. Naturwissen.*, 35: 12, 1942. As the result of difficulties in obtaining enemy publications, this excellent article did not come into the writer's hands until September, 1944.
7. HARVEY, W.: *Anatomical Examination of the Body of Thomas Parr*. This account was first published in the work of Dr. Betts, entitled; "*De Ortu et Natura Sanguinis*", 8 vol., London, 1669, the MS. having been presented to Betts by Mr. Michael Harvey, nephew of the author.
8. For the first searching critique of the supercentenarian myths see: THOMS, W. J.: *Human Longevity, Its Facts and Fictions*, London, Murray, 1873.
9. ZEMAN, F. D.: *The Pathological Anatomy of Old Age, An Historical Review*, in preparation.
10. STENDEL, J.: *op. cit.* p. 14.
11. SANCTORIUS, S.: *Medicina Statica, or Rules of Health*, London, 1676.
12. (a) GARRISON, F. H.: *History of Medicine*, ed., 4, Philadelphia, W. B. Saunders Co., 1929, p. 259.
- (b) MITCHELL, S. W.: *The Early History of Instrumental Precision in Medicine*, New Haven, 1892.

(c) GOTTFREDSEN, E.: Nicolaus Cusanus u. die Medizin, Muench. Med. Woch., 84: 1821, 1937.

13. VENNERS, TOBIAS: Via Recta ad Vitam Longam, London, 1620.

14. SYDENHAM, T.: The Entire Works of,; ed. 2, revised by John Swan, M.D., London, 1749, p. 60 and p. 617.

15. GARRISON, F. H.: op. cit., p. 260.

16. Ibid, p. 304 et seq.



## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Studies in the Pathogenesis of Experimental Dysentery Intoxication: Inhibition of the Lesions.*

A. PENNER AND A. I. BERNHEIM. *Gastroenterol.*, 1: 765, August, 1943.

The intravenous injection of Shiga toxin into dogs was previously found to produce certain definite anatomical changes in the gastro-intestinal tract as well as evidences of blood concentration. Ergotamine tartrate, administered intravenously in doses of 0.25 mg. per kg. one-half hour before the intravenous injection of the Shiga toxin, is found to prevent the appearance of the anatomical changes in the gastro-intestinal tract, and it inhibits the blood concentration which regularly followed the injection of the toxin. Since ergotamine tartrate prevents activity of the sympathetic nerve endings, we consider this inhibition by the drug as further evidence that the changes are caused by the activity of such motor endings. We consider that these sympathomimetic reactions represent adjustments which are necessary for the survival of the organism when its internal equilibrium is disturbed by disease.

*Hygiene of the Voice.* E. FROESCHELS. *Arch. Otolaryng.*, 38: 122, August, 1943.

In the speech of every day life as well as in professional speaking and singing, people frequently overcontract the muscles of the pharynx, mouth, and larynx. Especially in professional speakers and singers this habit may sooner or later destroy the voice (phonasthenia combined with pains, paresthesias, etc.). Children have shown this tendency to overcontraction. The hypercontractive state may be followed by weakness. The paper deals with the prevention and treatment of the "hyperfunctional" state. The so-called "chewing" method is the method of choice. It is based upon the common experience that one can talk and chew at the same time, which suggests an identity of the chewing and talking movements of the mouth. The patient is taught to think of chewing while talking. The results have been very favorable, in a large number of cases.

*The Visible Tuberculin Patch Test (A New Improvement).* M. GROZIN. *Am. J. Dis. Child.*, 66: 126, August, 1943.

The Tuberculin Patch Test as presently constituted is a "blind test" because it conceals the area of reaction while the patch is in place. There is no way of judging when the patch should be removed. If it is removed too early a positive reaction may be missed. On the other hand, if the patch remains on the skin too long, it may produce undesirable reactions.

To obviate these disadvantages the following improvement is suggested: three incomplete circles are cut on a strip of adhesive plaster, forming flaps or lids, with the lower poles acting as hinges. The outer lids are treated with tuberculin. The middle lid without tuberculin acts as a control. At various intervals the lids may be opened for inspection and then closed.

The advantages of the visible Tuberculin Patch Test are: 1) It makes it possible to observe the reaction while the patch is *in situ*. 2) Earlier diagnosis. 3) It avoids some local and systemic reactions resulting from prolonged contact of tuberculin and adhesive with the skin especially in those patients who are strongly allergic to tuberculin or sensitive to adhesive plaster. 4) In case of doubt the strip can be kept on the skin for a longer time instead of repeating the entire test. 5) It will facilitate the study of evolution and the latent period

of reaction to tuberculin and how they are influenced by drugs, chemicals, diseases, etc. 6) It is an individualized test. 7) It will aid in the making of a quantitative patch test. 8) It will be easier to interpret the reaction. 9) It will enable us to study the concentration and efficiency of various makes of tuberculin. 10) It can be easily modified according to individual needs and will therefore lend itself to use in research work.

*Prevention of Gangrene Following Ligation of Major Arteries—Experimental Study.* R. SPIEGEL, M. FRIEDLANDER, AND S. SILBERT. Surg., Gynec., & Obst., 77: 162, August, 1943.

Gangrene of the lower extremities is a frequent complication of aortic embolism at the bifurcation or after trauma to the major arteries of the lower extremities. Since the vascular bed peripheral to the site of interruption of the circulation is patent for a varying time after occlusion, we attempted to devise a method of delivering a nutrient fluid into the arteries distal to the obstruction.

To establish control situations in animals (cats and dogs), we developed a reliable technique for producing ischemic paralysis and gangrene by arterial ligation. Ligation of the three terminal branches of the abdominal aorta and of the anastomotic branches of the femoral arteries was most uniformly effective.

The principle of treatment is *autotransfusion* or shunt of blood from the animal's own blood vessel as *donor* to the distal portion of the femoral artery as *recipient*. Two types of autotransfusion were used: 1) The simpler method is the use of a donor artery, connected by means of a cannula in the central end of the donor, a connecting tube, and a cannula in the peripheral portion of the recipient artery. In a heparinized dog, the shunted blood flow was maintained for 11 hours and a pulse was palpable in the rubber tubing and in the femoral artery below the ligation. 2) The vein adjacent to the ligated artery was used as donor. Because of the negative pressure in the vein and the positive peripheral pressure in the recipient artery, a pumping machine was used to aspirate from the donor and deliver to the recipient vessel. The pipetting machine, which aspirates and expels fluid alternately in adjustable volume, was designed by the late Dr. Louis Gross.

The distal portion of the femoral vein was an inadequate source. Therefore the abdominal venous reservoir was tapped. (The abdominal veins and the innominate vein form a venous reservoir communicating with the portal-hepatic reservoir). The donor cannula was directed *centrally* in the femoral vein, passing under Poupart's ligament into the external vein. The blood was pumped into the contiguous femoral artery. The amount of blood to maintain nutrition was estimated on theoretical grounds and the machine was set to deliver this amount. The experiments were short term and were terminated after a run of two hours. The experiments were discontinued before we could work on a major problem, that of oxygenating the venous blood to be delivered to the artery.

*Frozen Shoulder: Periarthritis: Bicipital Tenosynovitis.* R. K. LIPPMAN. Arch. Surg., 47: 283, September, 1943.

The typical clinical aspects of periarthritis or frozen shoulder are reviewed with emphasis on the fact that though its duration is unpredictable the condition almost invariably terminates spontaneously in complete recovery. Surgical investigation on more than thirty cases of frozen shoulder has revealed the primary basic pathology to be in the long head of the biceps sheath and indicates that the subdeltoid bursa and musculo-tendinous cuff are not pathologically involved in this condition. Adhesive tenosynovitis extends from the sheath into the outer quadrant of the shoulder joint proper, but the entire inflammatory process subsides spontaneously when the tendon becomes firmly attached to the bicipital groove and its motion so obliterated. The pathological sequence underlying periarthritis provides a guide for the administration of conservative therapy and suggests a simple surgical approach when more rapid cure is desired. Motion pictures are presented illustrating the pathological condition of the biceps sheath as seen at operation as well as the operation for its repair.

*The Tuberculous Dental Periapical Granuloma.* R. H. BRODSKY AND J. S. KLATELL. *Am. J. Orthodontics & Oral Surg.*, 29: 9, 498, September, 1943.

This is a report of a study started in 1936 at the Sea View Hospital in New York City which included 362 tuberculous patients manifesting radiographic evidence of granulomata at the apices of teeth, and who were selected at random. It was felt that some of these blind abscesses might be specific tuberculous lesions, with the tubercle bacilli gaining entrance either through the dental pulp, by means of a hematogenous spread, or through deep periodontal pockets.

30 of the 362 specimens which were sectioned and studied by the pathologist were reported as having definite tuberculous pathology. One can conceive of the possibility of these residual tuberculous infections flaring up and becoming active foci.

*Occupational Acne.* L. SCHWARTZ AND S. M. PECK. *N. Y. State J. Med.*, 43: 1711, September, 1943.

Occupational acne is one of the most frequent forms of occupational dermatitis. It occurs among workers who are exposed to certain chemicals, which, when lodged in the pores of the skin, not only plug the openings and cause the retention of the secretions of the glands, but also act as stimulants for the formation of keratin and thus lead to comedo formation and occupational acne. Industries in which occupational acne occurs were investigated and clinical, physiologic and histologic studies were made of this disease. Occupational acne due to cutting oils, crude petroleum, coal tar, coal tar pitch, chlorinated naphthalenes, chloridiphenyls as well as chloridiphenyloxides were studied. Methods for prevention and treatment were given.

*Prostatitis Multiple Arthritis of Dental Origin.* H. A. GOLDBERG. *J. Am. Dent. A.*, 30: 1378, September, 1943.

In this paper the author wishes to call attention to the fact that no medical examination is complete without an oral and roentgenographic examination. Teeth and periodontal tissues harboring infection must be corrected before a complete medical diagnosis is made. This does not mean that all teeth harboring infection should be extracted. We, as dentists, know that infected teeth and gums can be treated and made serviceable indefinitely. The report in the *Medical Record*, February 7, 1940, on "The Relationship Between Dentistry and Urology, with Six Case Reports" by physicians of the College of Physicians and Surgeons, School of Dentistry, San Francisco, fairly well establishes the fact that dental foci may produce systemic disease.

*Constancy of Androgen Concentration in the Urine.* F. HOLLANDER, B. KRISS, E. KLEMPNER, AND R. T. FRANK. *Endocrinology*, 33: 217, October, 1943.

A study of androgen excretion in the urine was made over a period of about 30 days on 9 subjects with normal kidney function. The androgen was measured by the author's chick-comb assay technique. The results indicate that the concentration (e.g. units of androgen per liter of urine) of biologically active androgen in the urine is constant from day to day to within the error of the method used. The output of androgen in the urine varied, in these subjects, directly with the urinary volume. No correlation was found between the concentration of androgen and the urinary volume, even in the three members of the group whose urinary output was varied experimentally over a wide range by restricting and forcing fluid intake. This is contrary to the behavior of the other urinary constituents, in general, since their concentration has been observed to vary with the volume of urine. Further study of this problem is necessary before any definite conclusion can be drawn concerning kidney function in relation to androgen excretion.

*Cold Hemagglutination with Symmetric Gangrene of the Tips of the Extremities.* D. STATS AND J. G. M. BULLOWA. *Arch. Int. Med.*, 72: 506, October, 1943.

A case of symmetric gangrene of the tips of the extremities due to cold hemagglutination is described. Experimental studies revealed: (a) unilateral hemaglobinemia following

exposure of a forearm to cold, (b) hemagglutination in the capillaries of the conjunctiva due to cold and (c) absence of syphilis or evidence of a hemolytic anemia. No cause could be found to explain the presence of the cold hemagglutinin. A discussion is presented of clinical conditions in which transient or permanent arterial insufficiency of the extremities occurs despite adequate pulsation and absence of disease of the peripheral arteries. All the cases of cold hemagglutination reported in the literature in association with arterial insufficiency of the extremities or hemoglobinuria are tabulated.

*Clinical Observations on the Effect of 3,3'-Methylenebis(4-hydroxycoumarin)*. L. R. WASSERMAN AND D. STATS. *Am. J. M. Sc.* 206: 466, October, 1943.

The oral administration of 3,3-methylenebis(4-hydroxycoumarin) produces a marked fall (after a 24 to 72 hour latent period) in the prothrombin content and prolongation of the coagulation time of the blood in most patients. There is great variability in the degree of response to this drug. A definite fixed dosage schedule cannot be made. Patients must be individualized. There is danger of hemorrhage when the prothrombin index falls to 20 per cent of normal. Further trial of the drug is required before its use can be recommended in thromboembolic conditions.

*Cerebral Aneurysm and Massive Non-traumatic Cerebral Hemorrhage*. J. H. GLOBUS assisted by R. S. GLOBUS. *J. Neuropath. & Exper. Neurol.*, 2: 365, October, 1943.

Ten cases of ruptured cerebral aneurysm with consequent intracerebral and fatal intraventricular hemorrhage are reviewed clinically and anatomically.

The material surveyed yields a most significant observation. It demonstrates that softening of brain tissue results from the effects of an aneurysm of a neighboring cerebral blood vessel and concomitant alterations in its branches. This condition initiates a series of pathologic changes in the brain tissue paralleling the progressive disease alterations in the aneurysmal wall which culminates in rupture of the aneurysm. The escaping blood finds its way into the neighboring previously softened brain tissue. Thence the blood, still under the influence of arterial pressure, breaks through a residual zone of partially softened tissue, separating the so-called hemorrhagic cavity from the adjoining compartment of ventricular cavities and floods the latter as the fatal termination.

This observation discloses an obviously discouraging feature of cerebral aneurysm, one which has received little recognition, and which is responsible for many a surprising fatal termination in an otherwise promising clinical course.

Out of 20 verified cases of cerebral aneurysm a fatal issue occurred as a result of consequent intra-cerebral and intraventricular hemorrhage in ten cases. Surgical intervention in cerebral aneurysms is a highly hazardous undertaking. In the great majority of instances, the aneurysm is congenital in origin and not acquired as a result of hypertension or arteriosclerosis, while syphilis seems to play a rather insignificant rôle. Focal signs are rare, but there is one fairly constant finding: it is the inequality of pupils with the larger pupil on the side of the hemorrhagic lesion.

*The Fluorescence of Vitamin A*. H. SOBOTKA, S. KANN, AND E. LOEWENSTEIN. *J. Am. Chem. Soc.*, 65: 1959, October, 1943.

The fluorescence of vitamin A esters in alcoholic solution first increases, then decreases under continued ultraviolet irradiation. Both processes are of photochemical nature, but the second one is impeded by flushing with inert gases. The phenomenon is shown by vitamin A<sub>2</sub> ester, but not by the free vitamin A alcohol.

*Studies on Ionone. I. Cleavage of Ethyl Ionylidene Acetate*. H. SOBOTKA, E. BLOCH AND D. GLICK. *J. Am. Chem. Soc.*, 65: 1961, October, 1943.

The carbonyl compound obtained from the so-called barium  $\beta$ -ionylidene acetate by dry distillation with barium formate was found to be identical with  $\alpha$ -ionone. The same cleavage occurs in the case of barium  $\alpha$ -ionylidene acetate. This explains various failures to synthesize vitamin A reported in the literature.

*The Hyperkinetic Diseases.* E. MOSCHCOWITZ. *Am. J. Med. Sc.*, 206: 576, November, 1943.

The concept is submitted that certain diseases that may be called "hyperkinetic" represent primary exaggerations of normal bodily functions with morbid anatomic changes as a sequel, instead of the usually accepted reversed order of disease process. Tentatively, the following diseases are submitted: (1) Hypertension of the greater circulation, which represents an exaggeration of the normal intra-arterial pressure and leads to arteriosclerosis and the cardiovascular-renal syndrome. (2) Graves' disease, which represents, in greater part at least, an exaggeration of the normal basal metabolic rate. (3) Peptic ulcer, in which one of the dominant expressions is the exaggerated acidity and secretion of the normal stomach. (4) Cardiospasm, which represents an increase in the normal tone of the cardiac sphincter. (5) "Spastic colon," mucous "colitis" and ulcerative colitis, which represent exaggeration of the normal tonicity, peristalsis and secretion of mucus of the colon. (6) Manic-depressive psychosis, which represents an exaggeration of a normal rhythm. (7) Paranoia, which represents an exaggeration of the affective functions.

The biology of these diseases is discussed and possible mechanisms and new approaches are suggested. These maladies have certain common denominators. They possess a constitution that is usually a combination of phenotypic and genetic characters. The direct stimuli are maladjustments between the psyche and the environment. These diseases are essentially limited to the human species and are mostly products of civilization. Experimentally, they cannot be reproduced in animals except by methods that are unphysiologic for human beings. They rarely occur before the emotive faculties are fully developed. They possess a remarkable tendency to recur. Because the transition from the normal to the abnormal is gradual, no specific diagnostic test is applicable, unless it is an arbitrary one. The diagnosis therefore must depend upon a study of the composite picture—the organ—personality. These diseases, as a rule, evolve through 5 stages: (1) constitution; (2) exaggeration of function; (3) a lability of signs and symptoms; (4) fixation of this exaggeration of function; (5) somatic changes.

*Association of the Virus of Lymphocytic Choriomeningitis with Erythrocytes of Infected Animals.* G. SCHWARTZMAN. *J. Bact.*, 46: 5, 482, November, 1943.

There occurs a firm association of the virus of lymphocytic choriomeningitis with the erythrocytes of infected mice and guinea pigs. The ability of the virus to enter into this association markedly depends on the virulence of the strain for the animal species infected. Consistent infectivity of the erythrocytes is observed when the strain is capable of eliciting in the animal species a severe and fatal infection.

*The Non-Surgical Treatment of Calcified Bursitis, a Definite Safe and Painless Method.* J. ECHTMAN. *M. J. & Rec.*, 156: 673, November, 1943.

The author insists that bursitis can be cured in at least 95 per cent of the cases. One must know, however, the exact effects of physical therapy modalities upon the pathology and pathologic physiology of the condition treated. The most important complications in bursitis are: the acute, severe pain, the calcium deposits, and adhesions. In his study of ionization, Eichtman observed that the magnesium ion exerts a favorable effect on the pain in bursitis. He also observed that, while short waves may cause absorption of calcium deposits, long waves are more effective. While short waves may cause absorption of adhesions, the effect of long waves is more certain. A special technique is here employed. If this fails he employs ionization followed by the interrupted sine wave current, a method which rarely fails.

#### ANNUAL REPORT OF THE MOUNT SINAI HOSPITAL

The printed Annual Report of the Hospital for the year 1944 is now off the press and available for distribution. Readers of the Journal may obtain a copy by addressing a request to the Director of the Hospital.



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## THE RÔLE OF CASTRATION AS AUXILIARY TREATMENT IN CARCINOMA OF THE BREAST

### REPORT OF A CASE

BERNARD S. WOLF, M.D.

*[From the Department of Radiotherapy]*

As a result of the contributions of Huggins (1) on the effect of orchidectomy in cases of metastatic carcinoma of the prostate, interest has been revived in indications for castration in malignant tumors of both sexes. Bilateral oöphorectomy as auxiliary treatment in carcinoma of the breast was suggested by Schinzinger (2, 3) in 1889 and independently by Beatson (4-6) in 1896. Several surgeons (7-11) utilized this procedure and reported satisfactory palliative results in 25 to 45 per cent of the cases. The operative mortality in one report was 2 per cent (3); in another report, 6 per cent (10). With the general adoption of radical mastectomy and the introduction of X-ray castration, bilateral oöphorectomy fell into disuse. Horsley (12) has, however, recently added bilateral oöphorectomy to radical mastectomy in the treatment of young women with mammary carcinoma.

X-rays were first employed in gynecology to produce castration in cases of carcinoma of the breast by Foveau de Courmelles (13) in 1904. Wintz (14, 15) in Germany has used this procedure routinely since 1920.

As pointed out by Ahlbom (16), it is extremely difficult to obtain satisfactory statistical evidence on the effect of castration in cases of malignancy of the breast. Case reports, in which beneficial castration results cannot be doubted, are, therefore, valuable in defining the indications for this procedure (17-28). The following is such a case.

### CASE REPORT

*History:* T. C. (Adm. #486899), a German housewife, aged 42 years, was admitted to The Mount Sinai Out-Patient Department in February 1942. There was no history of cancer in her parents, two sisters, or other members of her family. Menses began at the age of 14, recurred regularly every four weeks, lasted five days with moderate bleeding, and were usually associated with slight pelvic pain and occasionally with some fulness of the breasts. Her first pregnancy, at the age of 20, terminated at six months in a premature delivery without apparent cause. A second pregnancy, a year later, resulted in the birth of a full-term infant. About two years after the birth of this child, the patient complained of pelvic pain and leucorrhea. A right salpingectomy was performed for a "pus tube." Following this operation, there were no menopausal symptoms but the patient was unable to become pregnant again.

In 1934, at the age of 34, the patient noted a small lump in her left breast. Six weeks later, a radical mastectomy was done. At the end of the operation and before closing the skin, the surgeon removed a mass of fat from the abdominal panniculus and placed it in the wound bed. The cosmetic result of this plastic procedure was satisfactory. The implanted mass of fat formed a pseudo-breast which was not much smaller than the normal right breast.

The patient's chief complaint on this admission was cough for one year productive of a small amount of mucoid sputum. On questioning, she stated that the mass of fat, which

had been implanted in the subcutaneous tissue of the left chest wall eight years before, had become very hard and slightly larger during the previous month. In addition, lobules which the patient had always been able to feel separately in the pseudo-breast had become confluent.

*Examination:* At the usual site of the left breast, there was a prominent hemispherical mass about four inches in diameter, elevated about two and a half inches above the level of the chest wall (fig. 1). This mass was stony-hard and firmly fixed both to the skin and the underlying thoracic cage. The nipple was absent. A long, well-healed oblique mastectomy scar extended into the axilla over the lower portion of the mass. The right breast, both axillary and cervical regions showed no evidence of tumor. A well-healed transverse suprapubic scar was present. The uterus was of average size; the right adnexal region was thickened. A flat purplish naevus "present since birth" covered the left shoulder.

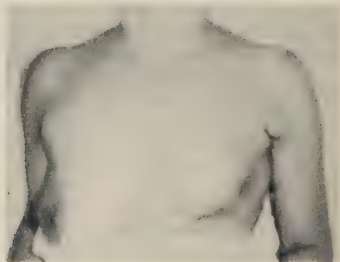


FIG. 1. Appearance of recurrent breast carcinoma when first seen in February, 1942. The mass at the site of the resected left breast was stony-hard throughout.

*Laboratory data:* The radiographic examination of the chest showed a homogeneous, somewhat triangular density behind the heart (figs. 2 and 3). The heart and mediastinum were displaced slightly to the left. A biopsy of the chest wall mass was reported as "carcinoma simplex."

It was clear that the patient had a huge, slowly growing, recurrent carcinoma of the breast. The question of therapy was discussed with the chest and surgical services. Their opinion was that excision of the portion of the thoracic cage including the tumor was feasible and offered some hope of a good result, provided the X-ray findings in the chest did not indicate the presence of metastases. The impression of the roentgenologist was that the shadow behind the heart might represent a collapsed left lower lobe. Because of these circumstances, it was considered advisable to explore the left pleural cavity.

*Operation* (March 17, 1942): An exploratory thoracotomy was performed. Numerous nodules were found in the parietal and visceral pleura and in the pericardium. The left lower lobe was shrunken and, within it, there was a hard mass about two inches in diameter. Biopsy of one of the nodules was reported as "metastatic carcinoma simplex."

*Postoperative course:* The wound healed without incident. Shortly after operation, hoarseness was noted and laryngeal examination revealed paralysis of the left vocal cord.

*Radiotherapy:* The first course of radiotherapy, was directed to the treatment of the mass in the mediastinum behind the heart since the patient's symptoms appeared to be due to the disease at these sites. One month after thoracotomy, radiotherapy was begun. Two anterior and two posterior mid-line mediastinal fields, each 10 x 15 cm., were treated with the following factors: 200 k V<sub>p</sub> (Villard circuit), filtration equivalent to 1.0 mm. Cu and 3.0 mm. Al, half-value layer 1.25 mm. Cu, target-skin distance 50 cm., 23 r per minute,



FIG. 2. Radiograph taken in March, 1942, showing the mass behind the heart. There was temporary delay to the passage of the barium mixture through the esophagus. The left main bronchus appears elevated.

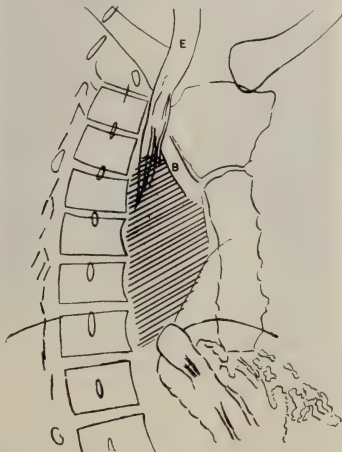


FIG. 3. Line drawing of figure 2. E denotes the esophagus; B denotes the left main bronchus.



cones diaphragmed at the skin. After 1400 roentgens (measured in air) had been administered to each field in a period of twelve weeks, treatment was discontinued at the request of the patient to allow her to leave the city. It should be noted that no direct radiation was



FIG. 4. Appearance of recurrent breast carcinoma fourteen months after radiation castration. The prominence above the puckered area is very soft and feels like the mass of implanted fat.



FIG. 5. Radiograph fifteen months after radiation castration showing distinct decrease in size of the mass behind the heart, no delay to the passage of the barium mixture and a more vertical course of the left main bronchus.

given to the external chest wall mass and that the amount of radiation scattered into this mass was small since all portals were directed toward the mediastinum and were carefully diaphragmed.

*Course:* The patient ran a slow but definitely downhill course after radiotherapy to the mediastinum was discontinued. The mass in the skin and subcutaneous tissue of the left chest wall increased in size; cough became marked and more productive; severe pain appeared in both sides of the chest. The patient lost twenty pounds in weight in about six months and complained of weakness and general malaise.

*Radiation castration:* In October, 1942, it was decided to castrate the patient with X-rays. The pelvis was treated through an anterior and a posterior field, each 15 x 15 cm. A total of 600 roentgens (measured in air) was delivered to each field within four days with the following factors: 200 k V<sub>p</sub> (Villard circuit), filtration equivalent to 0.75 mm. Cu and 1.0 mm. Al, half-value layer 1.2 mm. Cu, target-skin distance 80 cm., 13 r per minute, cones diaphragmed at skin. At the time of castration, the palpable mass was more than five inches in diameter and elevated at least three inches.

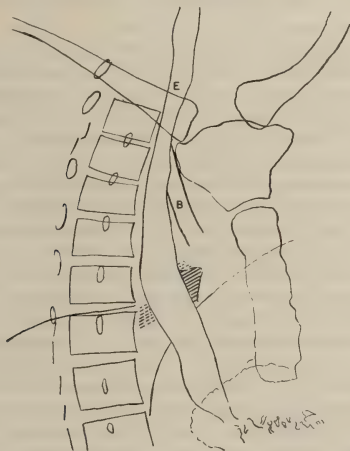


FIG. 6. Line drawing of Figure 5

*Post-castration course* (to February, 1944): Two weeks after pelvic irradiation, the patient had a regular menstrual period, but has been amenorrheic since then. About a month after pelvic irradiation, moderately severe hot flushes appeared.

On re-examination two months after castration, there was no doubt that the chest wall mass was decreasing in size. Chest pain and cough had disappeared. The decrease in size of the palpable mass continued until it was only about a fifth of its size at the time of castration (fig. 4). Fixation to the thoracic cage disappeared. In addition, the general condition of the patient improved rapidly and remarkably. She gained twenty-five pounds in six months and weighs more now than she ever did. She feels perfectly well and carries on full normal activity. Re-examination of the chest fifteen months after castration showed remarkable diminution in the size of the shadow behind the heart (figs. 5 and 6).

#### DISCUSSION

On the basis of truly amazing palliation resulting from castration in individual cases such as the one reported above, several authors (3, 12, 21, 27-31) have

suggested that this procedure be used routinely in all cases of carcinoma of the breast if the patient is still menstruating. The indications for the use of castration would then be 1) a mammary carcinoma with or without metastases and 2) the presence of menstruation. Both of these indications must however be examined critically on the basis of present available evidence.

There is convincing evidence, both clinical (32) and experimental (33-38) that castration, if done sufficiently early in life, can prevent the appearance of a breast carcinoma in many cases. This, however, cannot be interpreted as evidence indicating that, after a carcinoma has developed, castration can prevent recurrences or metastases. Cori (35) concludes from his experiments on breast carcinoma in mice that "when the tumor is once established, the ovarian hormone seems to be without influence on the rate of growth of the tumor. This is shown by the fact that spontaneous tumors in previously castrated animals do not grow less rapidly than tumors developing in normal animals." Marsh (36), from similar experiments, states that ovarian function is "evidently not necessary at that stage during which the tumor becomes visible or palpable, nor to subsequent growth." No experimental endocrine procedure has been found which will cause regression of a mammary cancer. Even hypophysectomy, with subsequent ovarian and adrenal atrophy, does not interfere with the growth of mammary cancer in mice (39). It is the clinical evidence of the cases described rather than any experimental evidence which proves that castration may cause regression of a breast carcinoma or its metastases in women. There is, however, no clinical evidence that this effect is permanent. No one claims to have produced a cure, either by surgical (10) or radiation (26) castration. If castration could prevent recurrences or metastases, the results of radical mastectomy should be better after the menopause and in women who have had both ovaries removed some time previously for an unrelated condition. Nathanson and Welch (40) point out that "the close correspondence (in the survival rates) of the group aged forty to forty-eight, most of whom are premenopausal, with the group forty-nine to sixty, the majority of whom have passed the menopause, is quite remarkable." Taylor (41) believes that his series of cases indicates that, other things being equal, "age and menstrual status do not affect the curability of the radical operation." Harrington (42) compared the results of radical mastectomy in a large series of cases from the Mayo Clinic with the results in a group of sixty-seven women who had undergone bilateral oophorectomy at least one year previous to mastectomy and found no "material difference." In fact, if only patients without axillary metastases were compared, the results were less satisfactory in the ovariectomized group. As far as can be determined at the present time, therefore, the absence of ovarian activity does not increase the survival rate and cannot be considered of prophylactic value.

During the period in which castration produces "growth restraint," it is possible that new metastatic foci are not formed or, if formed, do not grow to clinically detectable size. It might be argued that the routine use of castration is justified if the clinical appearance of a recurrence or metastasis can be postponed even if it cannot be prevented. This would be a valid argument if castration

were less effective after the recurrence or metastasis had appeared. On the contrary, the case reports demonstrate the most striking effects when obvious metastases are present and also that these effects occur rapidly, usually within a month. This is true also of surgical castration (7, 11). It appears, therefore, that castration may be safely postponed until recurrent or metastatic disease is present.

The problem of the optimum time to use castration would be simple if it were possible to determine, perhaps by hormone assays, the circumstances under which good results might be expected in any particular case. No definite endocrine abnormality has as yet been found in these cases (43-46). Unfortunately also, the cases helped by castration have shown no distinguishing clinical characteristics.

Another argument in favor of routine castration is the danger that a carcinoma may appear in the remaining breast if the patient should become pregnant (47, 48). Not all observers, however, forbid pregnancy indefinitely. Adair and Meltzer (49) believe that the danger of a subsequent pregnancy has been overrated. Haagensohn and Stout (50), on the basis of their own cases as well as the large series of Harrington, allow patients with a favorable prognosis to become pregnant. Fried and Goldberg (51) allow pregnancy if the patient has survived five years without evidence of disease. Moreover, as a pregnancy prophylactic, routine contraceptive measures rather than routine castration are preferable.

The second indication for the use of castration, i. e., the presence of menstruation, is also not entirely satisfactory as the sole criterion for the presence of ovarian activity. Estrogenic substances in appreciable amounts may be found in the blood and urine for some time after a spontaneous menopause (52), sometimes in a cyclic fashion (53). The vaginal epithelium may not cornify or lose its glycogen for many years (54, 55). Proliferative endometrium may occasionally be found after a spontaneous menopause. Considerable time usually elapses after the menses cease before the uterus and external genitalia atrophy. It is not surprising, therefore, that satisfactory, though less striking, palliation has been obtained after the menopause by radiating or removing the ovaries. In the series reported by Dresser (20), 48 per cent of the postmenopausal group obtained some relief from pain due to bone metastases. In Ahlbom's series (16), the results of castration appeared to be slightly better after the menopause. In the surgical series collected by Thomson (9), there were three cases of women seventy years old in whom good palliation was obtained. Therefore, in the absence of menses, the decision as to whether ovarian activity is present must be based on all available evidence, clinical and laboratory. If there is any doubt, pelvic radiation should be given since the dose required is small and the procedure harmless.

Clinical and hormonal studies have not shown any essential difference between surgical or radiation castration (52, 54, 56). After either of these procedures, a small amount of estrogenic substance continues to be excreted in the urine. Most investigators believe that the source of this estrogen is probably the adrenal under stimulation of the hypophysis. In castrate mice, adrenal hypertrophy

may occur (57, 58). Radiation of the adrenals and the hypophysis has been suggested, but there is as yet no evidence that this is of value (22).

Since castration is sometimes palliative, it was natural to investigate the effects of androgens. Animal experiments indicate that androgens produce hypertrophy and proliferation of the mammary gland in both sexes (59-65). The clinical effects of testosterone in metastatic carcinoma of the breast appear to be harmful in large dosage and without significant effect in small dosage (66). The use of androgens, therefore, seems to be definitely contraindicated.

In male patients with metastatic carcinoma of the breast, there is clinical evidence that orchidectomy even in apparently senile individuals, may give excellent palliation similar to castration in females (67). Estrogens are however contraindicated.

#### SUMMARY

It is suggested that, at present, the best indications for the use of castration in women with carcinoma of the breast are 1) the presence of active disease and 2) clinical or laboratory evidence of ovarian activity. A spontaneous menopause does not exclude the possibility of satisfactory palliation. In males with carcinoma of the breast and active disease, orchidectomy is indicated. Androgens and estrogens are contraindicated in both sexes.

#### BIBLIOGRAPHY

1. HUGGINS, C.: Effect of Orchiectomy and Irradiation on Cancer of the Prostate. *Ann. Surg.*, 115: 1192, 1942.
2. SCHINZINGER: *Chir. Kongress* 1, 28, 1889.
3. ———: *Das Karzinoma der Mamma*. München. med. Wchnschr., 52: 1724, 1905.
4. BEATSON, G. T.: On the Treatment of Inoperable Carcinoma of the Mamma. *Lancet*, 2: 104 and 162, 1896.
5. ———: The Treatment of Cancer of the Breast by Oöphorectomy and Thyroid Extract. *Brit. M. J.*, 2: 1145, 1901.
6. ———: The Treatment of Operable and Inoperable Carcinoma of the Mamma. *Glasgow, M. J.*, 74: 161, 1910.
7. BOYD, S.: On Oöphorectomy in Cancer of the Breast. *Brit. M. J.*, 2: 1161, 1900.
8. HERMAN, G. E.: Four Cases of Recurrent Mammary Carcinoma Treated by Oöphorectomy and Thyroid Extract. *Brit. M. J.*, 2: 1167, 1900.
9. THOMSON, A.: Analysis of Cases in which Oöphorectomy was performed for Inoperable Carcinoma of the Breast. *Brit. M. J.*, 2: 1538, 1902.
10. LETT, H.: An Analysis of 99 Cases of Inoperable Carcinoma of the Breast treated by Oöphorectomy. *Lancet*, 1: 227, 1905.
11. REYNÈS, M.: Traitment d'une Tumeur Inoperable du Sein par la Castration Ovarienne. *Gaz. d. hôp.*, 94: 394, 1921.
12. HORSLEY, J. S.: Recent Advances in the Study of Cancer. *South. M. J.*, 36: 8, 1943.
13. FOVEAU DE COURMELLES: Action Atrophique Glandulaire des Rayons X. *Compt. rend. Acad. d. sc.*, 140: 606, 1909.
14. WINTZ, H.: Die Roentgenbehandlung des Mammakarzinoms. Leipzig, Georg Theme, 1924.
15. ———: Ergebnisse der Behandlung von Unterleibskrebsen mit Roentgenstrahlen. *Strahlentherapie*, 69: 1, 1941.
16. AHLBOM, H.: Castration by Roentgen Rays as an Auxiliary Treatment in the Radiotherapy of Cancer Mammæ at Radiumhemmet, Stockholm. *Acta radiol.*, 11: 614, 1930.



17. DALAND, E. M.: An Analysis of Cases at the Ponds ville Hospital during its First Two Years. *Am. J. Cancer*, 15: 2359, 1931.
18. HOFFMAN, W. J.: Spontaneous Disappearance of Metastatic Nodules from Carcinoma of Breast, Following Irradiation of Ovaries. *Surg. Clin. North America*, 13: 494, 1933.
19. ROEMER, J.: Roentgentherapy in Metastatic Bone Cancer, with Report of Four Cases. *Radiology*, 22: 499, 1934.
20. DRESSER, R.: The Effect of Ovarian Irradiation on the Bone Metastases of Cancer of the Breast. *Am. J. Roentgenol.*, 35: 384, 1936.
21. SMITH, G. E.: Sterilization in Carcinoma of the Breast. *Am. J. Roentgenol.*, 36: 65, 1936.
22. CLARKSON, W., AND BARKER, A.: Five Year Cure of Mammary Carcinoma with Multiple Metastases to Bone. *Am. J. Roentgenol.*, 36: 615, 1936.
23. MARTIN, C. L.: Relation of Endocrine System to Malignancy. *Am. J. Roentgenol.*, 36: 314, 1936.
24. HUNT, H. B.: Regression of Pulmonary Metastases from Mammary Carcinoma Following Inactivation of Ovaries by Irradiation. *Radiology*, 34: 235, 1940.
25. ARCHER, V. W., AND COOPER, G. JR.: Regression of Carcinoma of the Breast following Artificial Menopause. *Am. J. Roentgenol.*, 44: 108, 1940.
26. DONALDSON, S. W., AND SILVERMAN, I.: Radiation Castration as an Auxiliary Treatment to Mammary Carcinoma. *Ohio State M. J.*, 37: 238, 1941.
27. POHLE, E. A.: Sterilization of the Ovaries by Roentgen Rays in the Treatment of Distant Metastases from Primary Carcinoma of the Breast. *Am. J. Surg.*, 54: 490, 1941.
28. HALBERSTAEDTER, L.: The Rôle of Artificial Menopause in the Treatment of Cancer of the Breast. *J. Internat. Coll. Surgeons*, 4: 435, 1941.
29. TAYLOR, G. W.: Artificial Menopause in Carcinoma of the Breast. *New England J. Med.*, 211: 1138, 1934.
30. WITHERSPOON, J. T.: Roentgen Irradiation of the Ovaries as Supplement to Surgical and Radium Therapy for Mammary Cancer. *Arch. Surg.*, 33: 554, 1936.
31. KAPLAN, I. I.: Radiation Therapy. New York, Oxford University Press, 1937.
32. HERRELL, W. E.: The Relative Incidence of Oöphorectomy in Women with and without Carcinoma of the Breast, *Am. J. Cancer*, 29: 659, 1937.
33. LATHROP, A. E. C., AND LOEB, L.: Further Investigations on the Origin of Tumors in Mice III. On the Part Played by Internal Secretion in the Spontaneous Development of Tumors, *J. Cancer Research*, 1: 1, 1916.
34. LOEB, L.: Further Investigations on the Origin of Tumors in Mice VI. Internal Secretion as a Factor in the Origin of Tumors. *J. Med. Research*, 40: 477, 1919.
35. CORI, C. F.: The Influence of Ovariectomy on the Spontaneous Occurrence of Mammary Carcinoma in Mice. *J. Exper. Med.*, 45: 983, 1927.
36. MARSH, M. C.: Spontaneous Mammary Cancer in Mice, *J. Cancer Research*, 13: 313, 1929.
37. MURRAY, W. S.: Some Effects of Ovariectomy during the Period of Declining Reproductive Powers in Mice, *J. Exper. Med.*, 63: 893, 1936.
38. WOOLLEY, G., FEKETE, E., AND LITTLE, C. C.: Mammary Tumor Development in Mice Ovariectomized at Birth. *Proc. Nat. Acad. Sc.*, 25: 277, 1939.
39. GARDNER, W. U.: Persistence and Growth of Spontaneous Mammary Tumors and Hyperplastic Nodules in Hypophysectomized Mice, *J. Cancer Research*, 2: 476, 1942.
40. NATHANSON, I. T., AND WELCH, C. E.: Life Expectancy and Incidence of Malignant Disease I. Carcinoma of the Breast, *Am. J. Cancer*, 28: 40, 1936.
41. TAYLOR, G. W.: The Rationale of Artificial Menopause in Carcinoma of the Breast. *Am. J. Roentgenol.*, 39: 419, 1938.
42. HARRINGTON, S. W.: Results of Radical Mastectomy in 5026 Cases of Carcinoma of the Breast. *Pennsylvania M. J.*, 43: 413, 1940.

43. YOLTON, N. AND REA, C.: Excretion of Androgens and Estrogens in Males with Mammary Carcinoma. *Proc. Soc. Exper. Biol. & Med.*, 45: 54, 1940.
44. ROSS, M. AND DOREMAN, R. I.: The Urinary Excretion of Estrogens and Androgens by Woman with Carcinoma of the Breast. *Cancer Research*, 1: 52, 1941.
45. TAYLOR, H. C., JR., MECKE, F. E., AND TWOMBLY, G. H.: Estrogen and 17-ketosteroid Excretion in Patients with Breast Carcinoma. *Cancer Research*, 3: 180, 1943.
46. HILL, B. R., AND LONGWELL, B. B.: Urinary Steroids from Breast Cancer Patients. *Endocrinology*, 32: 319, 1943.
47. KILGORE, A. R.: The Incidence of Cancer in the Second Breast. *J. A. M. A.*, 77: 454, 1921.
48. TROUT, H. S.: The Remaining Breast after Radical Removal of the Opposite Side for Carcinoma. *Surg., Gynec. & Obst.*, 34: 630, 1922.
49. ADAIR, F. E., AND MELTZER, A.: Personal Communications to Taylor, G. W. (41).
50. HAAGENSON, C. D. AND STOUT, A. P.: Carcinoma of the Breast II. Criteria of Operability. *Ann. Surg.*, 118: 859, 1943.
51. FRIED, J. R., AND GOLDBERG, H.: Frequency, Clinical Course and Treatment of Metastases from Cancer of the Breast. *Am. J. Roentgenol.*, 50: 499, 1943.
52. FRANK, R. T., GOLDBERGER, M. A., AND SALMON, U. J.: Estrogenic Substances in the Blood and Urine after Castration and the Menopause. *Proc. Soc. Exper. Biol. & Med.*, 33: 615, 1936.
53. FLUHMAN, C. F., AND MURPHY, K. M.: Estrogenic and Gonadotropic Hormones in the Blood of Climacteric Women and Castrates. *Am. J. Obst. & Gynec.*, 38: 778, 1939.
54. MACK, H. C.: The Glycogen Index in the Menopause. *Am. J. Obst. & Gynec.*, 45: 402, 1943.
55. McLAREN, H. C.: The Normal Menopause. *J. Obst. & Gynec. Brit. Emp.*, 48: 1, 1941.
56. ———: The Induced Menopause. *J. Obst. & Gynec. Brit. Emp.*, 48: 23, 1941.
57. WOOLLEY, G., FEKETE, E., AND LITTLE, C. C.: Effect of Castration in the Dilute Brown Strain of Mice. *Endocrinology*, 28: 341, 1941.
58. CRAMER, W. L.: Morphological Changes in the Mouse Adrenal and Their Functional Significance, with Specific Reference to the Hormonal Etiology of Breast Cancer. *Cancer Research*, 2: 723, 1942.
59. VAN HEUVERSWEYN, J., FOLLEY, S. J., AND GARDNER, W. U.: Mammary Growth in Male Mice Receiving Androgens, Estrogens and Desoxycorticosterone Acetate. *Proc. Soc. Exper. Biol. & Med.*, 41: 389, 1939.
60. KORENCHESKY, V., DENNESON, M., AND HALL, K.: The Action of Testosterone Propionate on Normal Adult Female Rats. *Biochem. J.*, 31: 780, 1937.
61. NELSON, W. O., AND GALLAGHER, T. F.: Some Effects of Androgenic Substances in the Rat. *Science*, 84: 230, 1936.
62. NATHANSON, I. T., AND ANDERVONT, H. B.: Effect of Testosterone Propionate on Development in Female Mice. *Proc. Soc. Exper. Biol. & Med.*, 40: 421, 1939.
63. JONES, E. E.: The Effect of Testosterone Propionate on Mammary Tumors in Mice of the C<sub>3</sub>H Strain. *Cancer Research*, 1: 787, 1941.
64. SELYE, H., McEWEN, C. S., AND COLLIP, J. B.: Effect of Testosterone on the Mammary Gland. *Proc. Soc. Exper. Biol. & Med.*, 34: 201, 1936.
65. NELSON, W. O., AND WERCKEL, C. G.: Effects of Androgenic Substance in the Female Rat. *Proc. Soc. Exper. Biol. & Med.*, 36: 823, 1937.
66. FARROW, J. H., AND WOODWARD, H. Q.: The Influence of Androgenic and Estrogenic Substances on the Serum Calcium in Cases of Skeletal Metastases from Mammary Carcinoma. *J. A. M. A.*, 118: 339, 1942.
67. ———, and ADAIR, F. E.: Effect of Orchidectomy on Skeletal Metastases from Cancer of the Male Breast. *Science*, 95: 654, 1942.

## THE ROLE OF INFECTION IN THYROID CRISIS

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Thyroid storm, though decreased markedly in incidence because of the advances in pre- and post-operative care of hyperthyroid patients, is still a complication which is occasionally seen and frequently dreaded. It is a fulminating increase in the symptoms of thyrotoxicosis, often with a rise in pulse rate up to 200; a marked increase in irritability, often progressing to delirium and even to coma; accompanied by marked and progressive weakness, which may go on to the point of collapse and death. The temperature usually climbs rapidly, sometimes reaching 106°F. or more. Vomiting and diarrhea have been noted on occasion. This description of the syndrome is given by Lahey (9, 10), Greene and Greene (7), Means (12) and Marine (11).

Thyroid crisis may occur in individuals who have not previously been considered as thyrotoxic (Dixon, 4). In patients with hyperthyroidism, it has been noted to occur without evident cause or after a slight incident, which would not affect a normal individual (Greene and Greene, 7; Lahey, 10). Bayley (1) reported eight cases of storm occurring after minor diagnostic procedures, such as paracentesis abdominis, lumbar puncture, or basal metabolism determination. Crisis has also been seen after operations other than thyroid surgery, such as tooth extraction, cystoscopy, appendectomy and hysterectomy (Bayley, 1; Ransom and Bayley, 13), and varicose vein injection (Greene and Greene, 6). Lahey (10) points out that severe emotional stimulation, such as the sight of a gruesome accident, or the death of a close relative, has been noted to precipitate acute hyperthyroidism.

It must be emphasized that the surgeons have noted that storms occur more frequently in patients in whom hyperthyroidism has been of long duration (Greene and Greene, 7). Ransom and Bayley (13) cite delay in admitting toxic patients to the hospital as an etiological factor in some of their group of fifty-one cases of crisis. Also, excessive surgery, or indiscriminate handling of the gland at the time of operation are causes of post-operative acute hyperthyroidism.

Clute (3) noted that the mortality increases with the percentage of one-stage operations. He stated that the unexpected deaths in crisis, in patients beyond the age of forty, usually occurred in those with a history of thyrotoxicosis of at least one year's duration, accompanied by marked weight loss.

Acute infection is a frequent cause of thyroid crisis (Lahey, 10; Greene and Greene, 7; and Ransom and Bayley, 13). Bayley (1) cites eight cases of crisis attributed to infection. Clute (2) reports nineteen deaths with storm, of which twelve patients had bronchopneumonia, and he stresses the frequency of this infection among patients dying from hyperthyroidism. In fact, he views bronchopneumonia as the secondary and terminal lesion in patients who are primarily overwhelmed by thyrotoxicosis.

Foss, Hunt and McMillan (5) reported post-mortem examinations on twenty-nine of ninety-six patients who died of thyroid disease. Death in nine of the twenty-nine autopsied cases, was not due to thyroid crisis, but to other conditions, namely: adenocarcinoma, four; cerebral hemorrhage, one; tracheal obstruction due to abductor palsy, one; diabetes mellitus, one; infarct of the lung, one; and secondary post-operative hemorrhage, one. Clinically, the cause of death in the remaining twenty patients was crisis. In nine of this group of twenty, an overwhelming infection preceded the storm. The infection in each

TABLE 1  
*Eighteen autopsied cases discussed*

| CASE NUMBER | AGE | SFX | THYROID OPERATION | OTHER SURGERY | STORM | TRACHEO-BRONCHITIS | PNEUMONIA | MAIN CAUSE OF DEATH                         |
|-------------|-----|-----|-------------------|---------------|-------|--------------------|-----------|---|
| 353179      | 23  | F   | 0                 | 0             | +     | 0                  | 0         | Storm                                       |
| 357952      | 56  | F   | 0                 | 0             | +     | +                  | 0         | Storm                                       |
| 384773      | 64  | F   | +                 | 0             |       | 0                  | +         | Storm                                       |
| 389159      | 28  | F   | 0                 | +             | ?     | 0                  | +         | Strep. hemol. bacteremia                    |
| 417510      | 58  | M   | 0                 | 0             | ?     | 0                  | +++       | Lobar pneumonia                             |
| 419004      | 56  | M   | +                 | 0             | +     | +                  | +         | Storm                                       |
| 427292      | 74  | F   | 0                 | 0             | +     | 0                  | +         | Storm                                       |
| 428550      | 40  | M   | 0                 | 0             | +     | +                  | 0         | Storm                                       |
| 433278      | 57  | F   | 0                 | 0             | +     | 0                  | 0         | Storm                                       |
| 434536      | 59  | F   | 0                 | 0             | +     | +                  | + + + +   | Storm & bronchopneumonia                    |
| 447605      | 48  | F   | +                 | 0             | +     | 0                  | +         | Storm                                       |
| 454296      | 64  | F   | 0                 | 0             | +     | 0                  | 0         | Storm                                       |
| 454865      | 55  | F   | 0                 | 0             | +     | +                  | + + + +   | Storm with massive atelectasis & bronchopn. |
| 459301      | 53  | F   | 0                 | 0             | +     | 0                  | +         | Storm                                       |
| 462360      | 65  | M   | +                 | 0             | +     | +                  | + + + +   | Bronchopneumonia                            |
| 468137      | 58  | F   | +                 | 0             | +     | +                  | + + +     | Bronchopneumonia                            |
| 509432      | 47  | F   | +                 | 0             | +     | 0                  | + + + +   | Shock & bronchopn.                          |
| 518758      | 59  | M   | +                 | 0             | ?     | +                  | + + + +   | Bronchopneumonia                            |

\* Partial excision of jugular vein.

of these nine cases was of sufficient degree to be considered the principal cause of death, and they were listed as follows: multiple abscesses of kidneys, acute bacterial endocarditis, streptococcus septicemia, acute purulent pericarditis, miliary tuberculosis, empyema, and in four instances—bronchopneumonia bilaterally. These observers attributed the death in the eleven remaining cases, in which no other lethal factor was identified, to "thyroid crisis."

In considering the relationship of infection to thyroid storm, it is interesting to note that Hahn (8) demonstrated that hyperthyroid rabbits were more susceptible than normal or hypothyroid animals to infection with virulent streptococci. Within an average time of forty-five hours, forty per cent of his normal and fifty per cent of his hypothyroid rabbits died. Within an average time of twenty-three hours, eighty per cent of the hyperthyroid rabbits

died. It is also significant that the hyperthyroid rabbits were much sicker than the members of the other two groups.

In reviewing the post-mortem material and the hospital records of the general service patients at The Mount Sinai Hospital between January 1, 1933 and July 1, 1944, it was found that there were eighteen autopsied cases which were considered clinically as deaths associated with thyroid storm (Table 1). In analyzing these cases, three must be separated from the group, because the clinical diagnosis of storm is questionable. All three had severe infections, which can give a picture not unlike that of thyroid crisis. One of the three patients (#417510) had a severe lobar pneumonia involving the right upper and lower lobes during the pre-chemotherapy era. A second had a streptococcus hemolyticus bacteremia, clinically attributed to a thrombophlebitis of the left jugular vein. At autopsy, this patient did not show such a lesion, and the focus of infection was not discovered (#389159). The third patient (#518758) presented the behavior of a patient in storm, but the fact that his pulse never rose above 120 and that he had a severe confluent bronchopneumonia of the right lower lobe with a small pneumonic area in the right upper lobe, was considered as evidence that the clinical picture was most probably due to infection rather than "crisis".

Of the remaining fifteen patients, all of whom were considered clinically to be definite instances of storm, twelve were females and three were males. The age distribution was as follows:

| <i>Age Group</i> | <i>Number of Patients</i> |
|------------------|---------------------------|
| 20-29            | 1                         |
| 30-39            | 0                         |
| 40-49            | 3                         |
| 50-59            | 7                         |
| 60-69            | 3                         |
| 70-79            | 1                         |

Though the small size of the group negates the statistical value of these figures, it is important to note that fourteen of these fifteen patients were above the age of forty. This agrees with the observation of Clute noted above.

Six of this group of fifteen were subjected to surgery and did not show any manifestations of crisis until the post-operative period.

At autopsy, ten of the fifteen patients had bronchopneumonia, which in five instances was of sufficient degree to be considered the chief cause of death. In ten of the fifteen, no significant infection or other adequate cause of death was noted at autopsy, and they must therefore be considered to have died of "crisis." Seven of the fifteen patients had tracheobronchitis. In all, there were only three of this group of fifteen, who at autopsy had no upper respiratory and no pulmonary infection.

#### COMMENT

In analyzing this material, it became apparent that there was a high incidence of respiratory tract infection in the small group of cases of thyroid storm which were studied. Two thirds of the group had pneumonia at post-mortem exam-



ination, and half of the pneumonias were of severe degree. Since only three of the fifteen had no respiratory tract infection, it seems fair to state that although infection is not always present in thyroid crisis, it is present frequently enough to warrant the employment of chemotherapy as an essential part of the treatment of storm. Furthermore, chemotherapy should be employed at the earliest indication of crisis.

#### CONCLUSIONS

1. The clinical picture of thyroid storm is reviewed.
2. Crisis is noted to be present much more frequently in patients beyond the age of forty.
3. Respiratory tract infection, frequently in the form of bronchopneumonia and occasionally in the form of tracheobronchitis, is a frequent, but not invariable, finding in patients presenting the clinical picture of thyroid storm.
4. This infection is sometimes severe enough to be considered the main cause of death.
5. Chemotherapy should be regularly included in the routine measures used in the treatment of thyroid crisis.

The writer acknowledges with deep appreciation the kind advice of Dr. Paul Klemperer.

#### BIBLIOGRAPHY

- 1) BAYLEY, R. H.: Thyroid Crisis, *Surg. Gynec. & Obst.*, 59: 41, 1934.
- 2) CLUTE, H. M.: The Operative Mortality in Hyperthyroidism, *J. A. M. A.*, 95: 389, 1930.
- 3) CLUTE, H. M.: The Unexpected Post-Operative Fatalities of Hyperthyroidism, *S. Clin. N. Amer.*, 11: 417, 1931.
- 4) DIXON, C. F.: Undiagnosed Hyperthyroidism, *Surg. Gynec. & Obst.*, 1: 118, 1930.
- 5) FOSS, HUNT AND McMILLAN: The Pathogenesis of Crisis and Death in Hyperthyroidism, *J. A. M. A.*, 113: 1090, 1939.
- 6) GREENE, E. I. AND GREENE, J. M.: Fatal Thyroid Crisis after Injection of a Varicose Vein, *J. A. M. A.*, 116: 611, 1931.
- 7) GREENE, E. I. AND GREENE, J. M.: Thyroid Crisis, *Ann. Surg.*, 95: 537, 1932.
- 8) HAHN, R. G.: Results of the Injection of Streptococci into Normal, Hyperthyroid and Hypothyroid Rabbits. *Medical Papers, Henry Christian Birthday Volume*, 742, 1936.
- 9) LAHEY, F. H.: The Management of Post-Thyroidectomy Complications, *Surg. Clin. N. Amer.*, 8: 13, 1928.
- 10) LAHEY, F. H.: The Crisis of Exophthalmic Goiter, *New England J. Med.*, 199: 255, 1928.
- 11) MARINE, D.: The Thyroid Gland, *Tice's Practice of Medicine*, 8: 241, 1942.
- 12) MEANS, J. H.: *The Thyroid and Its Diseases*, Philadelphia, Lippincott, 1937.
- 13) RANSOM, H. K. AND BAYLEY, R. H.: Thyroid Crisis, *West. J. Surg.*, 42: 464, 1934.

# A HITHERTO UNDESCRIBED ANOMALY OF THE EXTRA-HEPATIC BILE DUCTS AND BLOOD VESSELS AND ITS SURGICAL IMPLICATIONS\*

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It is the purpose of this article to present a hitherto unreported anomaly of the extra-hepatic bile ducts, both because it adds a new anatomical variation to the recorded literature and because it is the sort of configuration in which a serious operative injury might easily occur unless meticulous care is used in the dissection of the cystic pedicle.

The standard text books of anatomy (1, 2, 3) as well as the atlases (4, 5, 6) yielded little information concerning biliary tract abnormalities. The surgical and topographic anatomy texts (7, 8, 9) were likewise not helpful. Pathology texts and handbooks (10, 11, 12) were consulted, but the descriptions of biliary tract abnormalities were for the most part incomplete.

Numerous individual publications were consulted (13-30) and of these, the articles by Flint (13), Eisendrath (14, 15), Friend (16) and the elaborate reviews of Konjetzny (17) and Stolkind (18) were the most complete. Among the references consulted no abnormality of the biliary tract could be found which corresponded to the one about to be described.

## CASE REPORT

*History:* C. B., a 45 year old housewife, was admitted to The Mount Sinai Hospital on November 13, 1944 with the chief complaint of gall bladder disturbance for the past three years. This had started suddenly with a severe attack of what was diagnosed at that time as biliary colic. Since that time, indigestion, eructation and epigastric distress had been prominent and severe enough to cause her to seek relief. The patient had been on a fat free diet for the previous six months without any demonstrable amelioration of her symptoms. There had not been at any time any jaundice, weight loss or bowel disturbance. The patient was the mother of three children. The remainder of the history was non-contributory.

*Examination:* Physical examination revealed moderate tenderness in the right upper quadrant, but was otherwise negative.

In March 1944 roentgenologic studies of the gastro-intestinal tract, including a barium enema, were entirely negative. At this time, gall bladder studies revealed that the gall bladder filled well with the dye and concentrated, but that three filling defects were constantly present.

A diagnosis of chronic cholecystitis and cholelithiasis was made and operation was advised.

*Operation* (Dr. Garlock): Under gas-oxygen-ether anesthesia, an upper right rectus, muscle splitting incision was made exposing the gall bladder. A clamp was put on the fundus and gentle traction applied. At first the duct system appeared to be of the normal configuration except that the cystic duct seemed rather larger than usual, but not markedly so (fig. 1).

After beginning the dissection of the cystic pedicle, however, it became apparent that a radical deviation from the normal anatomy was present (fig. 2). The short cystic duct

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\* From the Surgical Service of Dr. John H. Garlock.

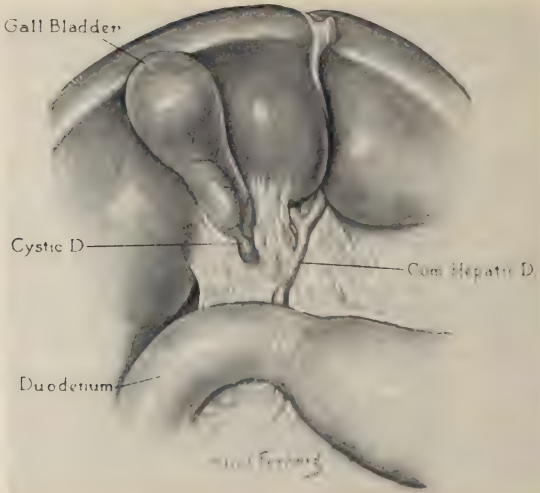


FIG. 1 Original view of the regional anatomy

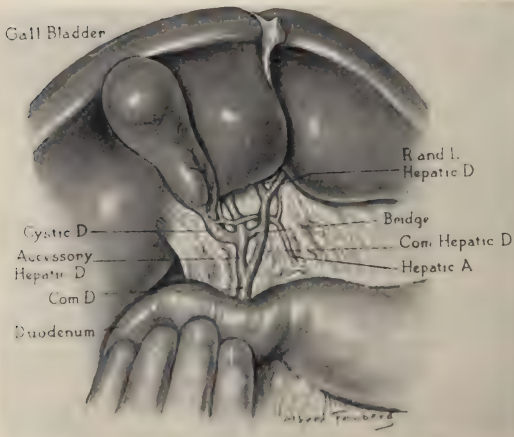


FIG. 2. After clarification of the regional anatomy

emptied into a large accessory hepatic duct and had no direct connection with the common hepatic duct proper. The right and left hepatic duct joined normally at the portal fissure and the common hepatic joined the accessory hepatic duct, which was approximately equal in size, about 3 centimeters above the ampulla of Vater. Two centimeters above the junction of the hepatic duct with the accessory hepatic duct there was a short bridge between the two. The calibre of this bridge was that of the hepatic duct, and it lay directly opposite the entrance of the cystic duct into the accessory hepatic duct. If figure 2 is inverted it will be seen that the anomaly resembles the figure "A," and it is suggested that it be called by that name, i.e., "A" type anomaly.

The hepatic artery crossed posterior to the common hepatic duct, anterior to the accessory hepatic duct, superior to the bridge described above, and traveled along the posteromesial border of the neck of the gall bladder. It gave off the cystic artery which could not have been more than 1 centimeter in length. The hepatic artery and accessory hepatic duct extended laterally and superiorly in close relation to the cystic duct and the neck of the gall bladder.

Pathologic study revealed that the gall bladder had numerous serosal adhesions, was thickened throughout, showed evidences of chronic inflammation, but had a relatively normal mucosa. It contained three gall stones.

#### DISCUSSION

From the above description and from figures 1 and 2, it is obvious that inadvertent injury of the hepatic artery, the accessory hepatic duct, or both, could easily have occurred. This case demonstrates the need for continual care in visualizing the biliary tract anatomy in each case before ligatures or clamps are applied. It also emphasizes the superiority of beginning the dissection in the region of the pedicle. Had an attempt been made to remove the gall bladder from the fundus downwards before dissecting out the cystic pedicle, it is not improbable that a clamp or ligature would have included some part of the hepatic artery or accessory hepatic duct where they lay in intimate contact with the cystic pedicle.

A study of the anatomical investigations by Flint, Eisendrath, and Friend reveals that it is not unusual for the hepatic artery to be intimately associated with the cystic pedicle and that accessory hepatic ducts as well may not infrequently lie in relation to this pedicle although in ways different than that described above. It is felt that the exact anatomy should be demonstrated in each case before the removal is initiated, or in other words, cholecystectomy should proceed from the neck upwards rather than from the fundus downwards.

#### SUMMARY

1. A previously unrecorded anomaly of the extra-hepatic bile ducts is presented.
2. The ease with which a severe injury might have been inflicted in the absence of meticulous dissection of the cystic pedicle is pointed out.
3. The need for immediate clarification of the biliary tract anatomy in each case before proceeding with cholecystectomy is emphasized.

#### BIBLIOGRAPHY

1. Cunningham's Text Book of Anatomy. ed. 8, New York, Oxford University Press, 1944.
2. GRAY, H.: Anatomy of Human Body. ed. 24, Philadelphia, Lea & Febiger, 1942.

3. MORRIS, H.: Human Anatomy. ed. 10, Blakiston Co., 1942.
4. SPALTEHOLZ, W.: Hand Atlas of Human Anatomy, Philadelphia, J. P. Lippincott Co.
5. SOBOTTA, J.: Atlas of Human Anatomy. ed. 5, New York, G. Stechert & Co., 1939.
6. GRANT, J. C. B.: An Atlas of Anatomy. Baltimore, Williams & Wilkins, 1943.
7. CALLANDER, C. L.: Surgical Anatomy, Philadelphia, W. B. Saunders Co., 1933.
8. MACGREGOR, A. L.: A Synopsis of Surgical Anatomy. ed. 4, Bristol, Wright and Sons, 1939.
9. CORNING, H. K.: Lehrbuch der Topographische Anatomie. J. F. Bergmann, Wiesbaden.
10. ASCHOFF, L.: Pathologische Anatomie. ed. 8, Jena, G. Fischer, 1936.
11. KAUFMAN, E.: Kaufman's Pathology. Philadelphia, P. Blakiston's Son, 1929, vol. 2.
12. HENKE, F. AND LUBARSCH, O.: Handbuch der Spez. Pathologischen Anatomie und Histologie, 1929.
13. FLINT, E. R.: Abnormalities of the Right Hepatic, Cystic and Gastroduodenal Arteries and of the Bile Ducts, Brit. J. Surg., 10: 509, 1922.
14. EISENDRATH, D. N.: Anomalies of the Bile Ducts and Blood Vessels, J. A. M. A., 71: 864, 1918.
15. EISENDRATH, D. N.: Injury of the Common and Hepatic Bile Ducts, S. G. & O., 31: 1, 1920.
16. FRIEND, E.: Abnormalities of Bile Ducts and their Blood Vessels and their Surgical Significance, Illinois M. J., 56: 169, 1929.
17. KONJETZNY, G. E.: Pathologische Anatomie und Physiologie der Gallenblasen und Gallengangserkrankungen, Ergeb. der Allgemein. Path. und Path. Anat. des Mensch. und der Tiere., 142: 712, 1910.
18. STOLKIND, E.: Congenital Abnormalities of the Gall Bladder and Extra-Hepatic Ducts, Brit. J. Child. Dis., 36: 115, 1939.
19. GRAHAM, E. A., COLE, W. H., COPHER, G. H., MOORE, S.: Diseases of the Gall Bladder and Bile Ducts. Philadelphia, Lea & Febiger, 1928.
20. THOREK, M.: Surgical Errors and Safeguards. ed. 4, Philadelphia, J. B. Lippincott Co., 1943.
21. BOHM, F.: Einfall von congenitaler Gallengangatresie mit Gallengangseyste. Zfst. für angewandte Anatomie und Konstitutionslehre., 1: 105, 1913-14.
22. RUGE, E.: Beiträge zur chirurgischen Anatomie der grossen Gallenwege, Arch. f. Klin. Chir., 87: 47, 1908.
23. SCHACHNER, A.: Anomalies of the Gall Bladder and Bile Passage, Ann. Surg., 64: 419, 1916.
24. BREWER, G. E.: Anatomy of the Gall Bladder and Bile Ducts, Ann. Surg., 29: 721, 1899.
25. WALTON, J.: Reconstruction of the Common Bile Duct, S. G. & O., 79: 57, 1944.
26. WILSON, G. E.: Bile Duct Strictures, S. G. & O., 68: 288, 1939.
27. ELIOT, E.: The Repair and Reconstruction of the Hepatic and Common Bile Ducts, S. G. & O., 26: 81, 1918.
28. MOVAT, T.: Lancet, London, 2: 181, 1938.
29. JACOBSON, J. H.: Tr. Am. A. Obst., 27: 183, 1914.
30. LADD, W. E. AND GROSS, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders & Co., 1941.



## A CASE OF CHRONIC METASTATIC ABSCESS OF THE COSTAL CARTILAGE DUE TO *BACILLUS PYOCYANEUS*

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[From the Surgical Services of Dr. H. Neuhof and Dr. A. Hyman]

*Bacillus pyocyaneus* (*Pseudomonas aeruginosa*) is an organism not uncommonly encountered in infected wounds of various types and is rarely of clinical significance. However, the organism is occasionally found in a blood stream invasion and may then be a dangerous pathogen. Infections of the genitourinary tract due to *B. pyocyaneus* are especially common, and transient bacteremias of this organism arising in the urinary tract are known to occur. Scott (1) in 1929 reported three positive blood cultures for *B. pyocyaneus* in 82 cases, when routine blood cultures were made after chills following urologic instrumentation. Hyman and Edelman (2) in 1932 reported one *B. pyocyaneus* blood stream infection in 63 cases of a similar series.

Invasion of the blood stream with *B. pyocyaneus* may be followed by localizing infections in any part of the body. Slutsky and Matlin (3) cited a case of *B. pyocyaneus* meningitis after a bacteremia following a pyelolithotomy. Fish and his associates (4) reported acute bacterial endocarditis due to *B. pyocyaneus* after repeated catheterizations and suprapubic prostatectomy. Schein (5) described a case of *B. pyocyaneus* osteomyelitis of the dorsal spine following cystoscopy for renal calculus. However, infections of the costal cartilages due to *B. pyocyaneus* can be regarded as rare. The following is believed to be such a case, namely, one of secondary invasion of the costal cartilage after a transient *B. pyocyaneus* blood stream infection arising from the urinary tract. The rare occurrence, the unusual features and the good result obtained by radical excision, merit the presentation of this case.

### CASE REPORT

*History.* L. M. (Adm. #513339) a male, aged 60 years, was first admitted to The Mount Sinai Hospital on October 23, 1943. He had been in good health until May 1943 when urinary frequency and nocturia were noted. These symptoms became progressively worse until October 1943, when the patient developed acute urinary retention. He consulted his physician who catheterized him, and obtained twelve ounces of residual urine. Two weeks later the patient noted hematuria, severe right flank pain and a rise in temperature. He then entered the hospital for treatment.

*Examination.* The patient was a well nourished but acutely ill elderly male. His temperature was 105°F.; pulse was 92. The chest was negative. The heart was not enlarged but auricular fibrillation was present. There was marked right costovertebral angle tenderness. The prostate gland was firm, smooth and enlarged to twice its normal size. The remainder of the general examination was essentially negative.

*Laboratory Data.* Urine contained 2 plus albumin, many white blood corpuscles and red blood corpuscles. Blood urea nitrogen was 15 mg. per cent. The blood Wasserman test was negative. A urine culture revealed *B. pyocyaneus*. A blood culture was positive for *B. pyocyaneus*. An electrocardiogram showed auricular fibrillation, but no other abnormalities.

*Operation.* After preliminary catheter drainage of the bladder for two weeks, the patient's temperature returned to normal. A first stage suprapubic cystostomy was then performed, at which time a prostatic abscess was discovered and evacuated. One month following the first stage procedure, a second stage suprapubic enucleation was performed.

*Postoperative course.* Following the second stage operation, the patient improved progressively. The suprapubic wound closed and the patient voided without difficulty.

During the postoperative period, the patient observed for the first time the spontaneous appearance of a tender swelling over the left lower anterior chest. Examination of the chest revealed the presence of a firm mass in the chest wall extending from the left anterior axillary line to the left parasternal line. The mass was ill-defined, not freely movable and merged into the surrounding soft tissue. It measured approximately  $4\frac{1}{2}$  inches in diameter. The skin overlying the mass was erythematous, tense and very tender.

Because of the appearance of the mass the past history was reinvestigated. The patient then reported that he had pain in the left anterior chest for the first time in May 1943. This coincided with the time of onset of urinary symptoms. The patient was unable to state whether the urinary or the chest symptoms occurred first. In June 1943 the patient sustained an injury to his left anterior chest with the resultant fracture of two ribs. This injury definitely occurred after the onset of the chest pain. During the next few months, chest pain was minimal. It became severe, however, during the period of hospitalization and was associated with the appearance of the already described swelling in the wall of the chest.

An attempt was then made to ascertain the nature of the unusual mass. X-ray of the chest, including the ribs, revealed no abnormalities. Aspiration was attempted, but only a few cubic centimeters of blood were obtained. Because of the diminution of chest pain, the patient was discharged to the care of his private physician.

*Second admission.* The patient was re-admitted to the hospital in January 1944, two weeks after his previous discharge, because of continued chest pain.

*Examination.* The suprapubic sinus was closed and well-healed. The swelling on the anterior chest was unchanged in its appearance from that observed during the previous admission. It was of approximately the same size and was still firm and tender. The overlying skin was adherent as in cancerous invasion.

*Laboratory data.* The blood examination showed: hemoglobin, 70 per cent; white blood cells, 6,750 with 80 per cent polymorphonuclear leucocytes. The urine contained many white blood cells but was otherwise normal. A blood Wasserman examination was negative. X-ray examination of the chest revealed no abnormalities in the lungs, but there was an irregular expansion of the anterior portion of the 10th rib on the left side in the region of the costochondral junction.

*Operation.* The preoperative impression of the chest wall mass was that it was a tumor arising from rib or costal cartilage and that it most likely was a chondrosarcoma or fibrosarcoma.

The operation was performed on January 7, 1944, by Dr. Neuhof. An incision was made in the left lower anterior chest wall directly over the site of the suspected tumor. A small portion of the mass was removed for biopsy. Frozen section performed in the operating room revealed only inflammatory tissue. Because it was thought that the suspected tumor was deeply invasive and that the segment removed for biopsy was not a representative one, a block excision of the tumor was decided upon. The original biopsy wound was then closed with heavy silk sutures. An elliptical incision was then made on either side of the tumor completely encircling the mass. The incisions were carried down to the chest wall. Segments of the 6th, 7th and 8th ribs on the left side were resected. The left pleural cavity was opened, and the tumor-like mass was inspected from its diaphragmatic aspect. It was found to be intimately adherent to the ribs at their costochondral junctions, and to the superior surface of the diaphragm. The tumor-like mass was excised by shaving it off the surface of the diaphragm. The wound was closed with interrupted silk sutures.

*Postoperative course.* The postoperative course was uncomplicated. The wound healed by primary intention. The patient was discharged asymptomatic 14 days after the operation.

*Pathology and Bacteriology Gross.* The specimen consisted of a portion of the chest wall. There was an oval piece of skin measuring 29 x 9 cm. The skin showed no gross changes. Attached to it were subcutaneous fat tissue and segments of three ribs from the left lower anterior chest. The upper two ribs measured 14 cm. in length and showed the usual architecture. The lower rib measured 9 cm. in length. At the site of the costochondral junction, there was thickening and induration. The soft parts immediately surrounding the junction were markedly thickened. On longitudinal section through the rib, a cavity was found at its medial end. The cavity was irregular, measured approximately 2 x 1.5 cm. and was lined by red, soft, granulation tissue. Its outer wall was made up of yellow-white, firm tissue. The cavity was empty except for a small amount of hemorrhagic and fibrinous exudate.

*Microscopic observations.* The histological studies disclosed a chronic abscess of costal cartilage with marked ossification. The suppurative process extended into the muscle. There was no evidence of neoplasm found in the specimen submitted. Bacteriology culture of the exudate in the center of the abscess cavity yielded a pure growth of *B. pyocyaneus*.

*Follow-up record.* The patient was seen in the Follow-Up Clinic in June 1944, 5 months after the operation. At that time he had no specific complaints related to his previous operation. The chest wound remained completely healed.

*Comment.* A case of abscess of the costal cartilage due to *Bacillus pyocyaneus* following blood stream infection from the urinary tract is described. This case is believed to be more or less rare in medical literature. Clinically, the infection of the cartilage simulated closely a tumor of the chest wall. Surgical extirpation was followed by recovery.

#### BIBLIOGRAPHY

1. SCOTT, W. W.: Blood Stream Infections in Urology. Report of Eighty-Two Cases. *J. Urol.*, 21: 527, 1929.
2. HYMAN, A. AND EDELMAN, L.: Medical and Surgical Aspects of Hematogenous Infections in Urology. *J. Urol.*, 28: 173, 1932.
3. SLUTSKY, N. AND MATLIN, P.: *Pyocyaneus* Meningitis. *J. A. M. A.*, 113: 1400, 1939.
4. FISH, G. W., HAND, M. M. AND KEIM, W. F., JR.: Acute Bacterial Endocarditis due to *Pseudomonas Aeruginosa* (*B. pyocyaneus*). *Am. J. Path.*, 13: 121, 1937.
5. SCHEIN, A. J.: *Bacillus Pyocyaneus* Osteomyelitis of the Spine. *Arch. Surg.*, 4: 740, 1940.

# ESSAYS ON THE BIOLOGY OF DISEASE<sup>1</sup>

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## CHAPTER 10

### RECENT ADVANCES IN PSYCHOSOMATIC MEDICINE

It appears presumptuous to speak of the advances in a field of medicine that is still in the embryonic stage. I propose rather to submit an essay and a summation of our current knowledge. Psychosomatic medicine as a matter of fact is nothing new; it is as old as Hippocrates. Its recent interest represents more a crystallization of centuries of thoughts than the discovery of new mechanisms of diseased processes. The reason why its renaissance has been so long delayed can be largely attributed to the teaching of mechanized methods of medicine in our colleges, traceable directly to the dominance of the Continental school in the past century which taught and still teaches that disturbances of function, which we call disease, always follow morbid tissue changes. But it is slowly but surely dawning upon us that the reverse is sometimes true and that morphological changes may be the result of disturbances of function which are largely conditioned by emotional factors, and that therefore morbid anatomy, chemical and humoral changes may sometimes be the results and not always the cause of disease. Curiously, this modern trend represents a reversal to the doctrine that Hippocrates taught, that a disease and the temperament cannot be divorced. It is satisfying to know that in recent decades there has been a decided trend in these habits of thought in our medical schools, and that psychiatry, not limited merely to the study of insanity, is receiving a larger share in the medical curriculum. This may be the reason why the study of psychosomatic medicine is largely within the hands of the youth of our profession.

What is a psychosomatic disease? It is not easy to define because we do not know where the "psyche" ends and the "soma" begins. Tentatively we may define a psychosomatic disease as one in which purely psychogenetic factors result in organic disease. Although organic disease has thus far not been discovered in the psychoses by methods at our command I would include them in the psychosomatic diseases because biologically they behave identically. There is no doubt that such changes exist in the psychoses, as proven by the recovery that occasionally results by physical or chemical means. As a matter of fact, the distinction between functional and organic, a concept that psychiatrists have viewed as inviolable for centuries, has been rudely jarred by the discovery that physico-chemical agents may profoundly modify abnormal behavior, and that

<sup>1</sup> This is the tenth in a series of essays by Dr. Eli Moschcowitz in which an attempt is made to interpret certain forms of chronic disease from the biologic viewpoint as opposed to the current trend toward rigid classification implying a concept of disease as a more or less static phenomenon.

According to present plans these essays will appear in consecutive issues of the *Journal of The Mount Sinai Hospital*. When the publication of the projected series of essays is completed, the several installments will be assembled and printed in the form of a monograph.—Ed.

the electroencephalogram may record what had hitherto been regarded as purely mental processes. The implications are enormous not only for a clearer approach to the study of mental processes but also for wider avenues for therapy. Freud (1) even in 1928 had an inkling of such an eventuality when he wrote "Because of the essential unity of the two things that we divide into somatic and psychic, one may prophesy that the day will come when the avenue from biology and chemistry to the phenomenon of neurosis will be open for our understanding and we hope also for therapy." The schism between vitalism and materialism is slowly breaking up. One may compare the psychiatry of today with chemistry and physics a century ago before the atomic theory. One may foster the wild hope that some day another Dalton and perhaps another Thomson may discover units of human behavior like the atom and the electron so that they may be interpreted in terms of physico-chemical reactions rather than as vitalistic processes.

Students of psychosomatic disease in their enthusiasm have lately included within this domain the effect of emotion on individuals with previously existing organic disease, for instance the excitation of pain by emotion in coronary disease. Nor may one include a reversal of the process; the study of the effect of somatic disease on the psyche; what one calls somatopsychic medicine. This is a fascinating and largely untouched field. In this sense, all medicine is psychosomatic or somatopsychic.

The definition we have given implies that physiological changes merge imperceptibly into organic disease. Heretofore, the terms "functional" and "organic" have been sharply dichotomized, because in the first, structural alterations are not found, while in the latter they are. What we really mean is that *thus far*, no structural changes have been found within the scope of our present resources. It is impossible to conceive of an abnormal physiologic change, a contraction of or dilation of a vessel or gut, an increase in gastric secretion, abnormal sweating, as instances, without some simultaneous tissue change. The difference between a functional change and an organic one is in reality a quantitative and not a qualitative one, and when one passes into the other is determined only by the limitation of our senses. That emotions may cause profound physiological changes that are even measurable, requires no argument. You are all familiar with Cannon's (2) concept of homeostasis in which these responses are viewed as defense mechanisms against pain, hunger, fear and rage. The term "emotion" is generic and includes many varieties. It certainly is not synonymous with "worry" an expression, unfortunately, that physicians who are not psychiatrically minded, use to describe every variety of emotion, and has even insinuated itself in some recent psychosomatic literature. Emotion may be fear, anger, distrust, anxiety, hate, rage, love, sorrow, joy, and the physiological response varies with the variety of emotion. Witness the blanching of the skin under the stimulus of fear, and the flushing that comes with joy, the suppression of sweating that comes with fear and its increase with aggression or vice versa. Wolff and Wolf (3) made some interesting observations on their famous Tom, their laboratory helper, who for 47 years fed himself through a gastrostomy opening, made for atresia of the



esophagus after swallowing hot clam chowder. When an episode arose that created fear in Tom or what Wolff and Wolf call an "alarm" reaction, the secretion of gastric juice ceased. On another occasion, when Tom felt aggression, the secretion increased to triple the normal. Hoelzel (4) recently reported interesting observations on his own gastric secretion. For reasons of his own he was in the habit of testing the acidity of his gastric secretion daily. Suddenly he received a threat that he might be shot, and during this episode his gastric secretion rose to appreciable heights; when the threat was abolished, the secretion returned to normal. Pavlov's experiments on the variety of reactions from different conditioning reflexes in dogs, contributes further illustrations. Unfortunately, in man, experiments on the excitation of a wide range of functions by different kinds of emotion are not feasible. Above all, it is not only the variety of emotion but the way in which "these emotions are experienced" as Stanley Cobb puts it, that determine the physiological response. Much of the current thinking on psychosomatic problems loses significance unless this is grasped. One individual trembles, the second vomits, the third gets palpitation, the fourth gets increased peristalsis, the fifth flushes, the sixth pants for breath, the seventh feels a lump in his stomach, and these symptoms are reflected in physical expressions such as changes in blood pressure, increase or suppression in gastric secretion, increase in blood sugar, increase in intestinal secretion and tachycardia. I am confident that if such individuals could be promptly x-rayed, they would also show spasm of the cardiac sphincter and pylorus and hyperperistalsis of the gastrointestinal tract. The internal secretions are probably profoundly affected by emotions, but proof by other than clinical observation is as yet unconvincing. Nor has any graphic precise evidence been submitted to prove that disordered functions become fixed under protracted emotional states, nor can one, for the present at least, visualize a method that will afford such evidence either in the human being or experimentally. Psychiatric problems unfortunately do not lend themselves, except in very limited circumstances, as in the case of Tom, to laboratory proof. The only way whereby we can surmise that such a fixation may take place is by noting the sequence of events by direct and prolonged clinical observation in the same individual. Happily, there are enough of these observations to make an impressive showing. Such observation is more within the scope of the general practitioner than of the consultant because the latter only sees a small cross section of the life cycle of the disease, and for the same reason, such studies cannot be made in hospitals, for here only one observes the terminal phases of disease.

It is therefore not only the variety of emotion, but the individuals' reaction to the emotion that are significant in the mechanism that leads to psychosomatic disease.

Sceptics reason thus: many persons, especially in these days of social and economic insecurity, are subject to severe emotional reactions, but only a few acquire psychosomatic disease. These critics have failed to grasp the fact that it is not the reaction itself, but the impact of this reaction on a particular kind of individual that not only conditions psychosomatic disease but also the variety that will

eventually manifest itself. In this respect, psychosomatic disorders may be aptly compared to deficiency disease or to infections. Duality in causation runs like a thread throughout medicine. It is not the bacterium, but the impact of the bacterium in a susceptible individual that makes him sick, and even in disorders that are not infectious we are beginning to think again in terms of constitution. To regard constitution as comprising only physical attributes is a narrow viewpoint. Pragmatically, especially in respect to the study of susceptibility to psychosomatic disease, one must evoke a broader concept of constitution. A constitution may be physical, it may be psychological, usually it is both. There is argument as to how much of the constitution is hereditary or genotypic, and to what extent it is the result of environmental or phenotypic factors. When the physical makeup is part and parcel of the constitution, there is evidence that this is hereditary. For example, the sthenic habitus that is frequently found in hypertensive families, the anthropomorphic characteristics that Draper has described in patients with peptic ulcer, are largely genetic in origin. There is also no doubt that sometimes the psyche is largely hereditary; the frequent hereditary nature of manic depressive psychosis and paranoia is a proof. However, evidence thus far does not permit us to say to what extent the complex of characteristics which we call personality is genetic or environmental. It would lead us too far afield to enter into this much belabored subject. In recent psychosomatic literature there is repetitious argument that because a malady is often familial that it is hereditary. No one can study personality traits in families without being impressed that the tone and life outlook of the family are profoundly influenced not only by the attitude of the parents, but by the reaction of the siblings toward each other, either by direct imitation or by compensatory reactions. The evidence derived from psychoanalytic techniques indicates strongly that personality and the resultant behavior are conditioned by influences that begin at birth. Observations on the development of personality in identical twins brought up under different surroundings are confirmatory. Unfortunately there are altogether too few observations on the occurrence of psychosomatic diseases in identical twins. In the only case I have been able to find reported by Friedman and Kassanin (5) hypertension occurred in one and not in the other. The twin brothers were entirely opposite temperaments.

The difficulty in classifying types of personality is obvious to everyone who is cognizant of the wide variety of classifications that have been devised. Kretschmar divides them into the pyknic, athletic and asthenic types. There are the introverts and the extraverts, and Jung has subdivided these into the thinking, feeling, sensuous and intuitive varieties. Freud has introduced the adjectives, narcissistic, obsessive, schizoid and hysterical. The terms represent dominant traits and in the hands of their sponsors have proved useful as a working guide for the classifications of the neuroses. Unfortunately, people are not just one thing or another like flowers or plants, but are aggregates of many qualities modified by their interreactions so that there is nearly always more or less overlapping. Nevertheless, despite the difficulties in classifying, many students in psychosomatic medicine are active in synthesizing broad personality types in

which particular psychosomatic diseases are more likely to occur than in others. Unfortunately, thus far in only a few of the psychosomatic diseases have these studies been attended with any measure of success. Thus in Graves' syndrome in which the type personality is more clear cut than in any other psychosomatic disease, the individual is of the sensitive emotional type, unstable, with manic-depressive trends. Usually, one can trace the sensitivity to parental overprotection in childhood, resulting very frequently in parental fixations. This accounts for the greater frequency of Graves' disease in females, since they are more subject not only to parental but to social overprotection. I have applied the term "allergic to life" to the life pattern of these individuals. It is obvious that such folk will react deeply to either sudden powerful insults or to reiterated smaller ones; under such circumstances, the Graves' syndrome sometimes arises either suddenly or insidiously. One sometimes hears of apathetic Graves' syndrome. If one digs deeper, this apathy is found to be only a mask. In other words, Graves' syndrome represents the resultant of the impact of environmental factors upon a constitutional background. Of the vast number of physiological reactions set forth by the impact of these two factors and of the biology of the psychosomatic diseases, I shall speak later. In sufferers with peptic ulcer, the dominant personality trait is a strong aggression. They are born fighters with strong sadistic and masochistic trends. As would be expected such individuals are usually intolerant; indeed they are all or nothing folk and strong and lasting haters. We all hate at some time or other in our lives; but most of us express our hate outwardly. Some of us do it with our fists, some by calling names and others by pity, but because of their repressions, ulcer people dam up their emotions and literally consume themselves with anger.

As in Graves' syndrome, one finds frequently that the symptoms were initiated by a psychological trauma, the illness or death of a dear relative, economic distress, marital maladjustment, etc. This factor has a strong bearing upon the high incidence of peptic ulcer in the allied armies, due to the inability of many recruits to adjust themselves to military life. If one may judge by the clinical sequence of events, this impact of environmental factors upon a type personality sometimes both initiates and activates a preexisting ulcer.

In non-specific ulcerative colitis on the other hand, the dominant personal characteristic is a spirit of defeatism. Such patients are mostly dependent folk, indecisive and self-pitying. Their sense of guilt is expressed outwardly; usually it is against an individual and not against a situation. I shall leave the symbolic interpretation of the diarrhea to the Freudians. I have never met a patient with non-specific ulcerative colitis who was what one may call successful in life. Individuals with peptic ulcer and essential hypertension are often successful; the victims of Graves' syndrome sometimes are, usually in the arts, literature, painting, music, etc. A neurosis is sometimes a useful commodity. In individuals with non-specific ulcerative colitis patient and persistent questioning can usually elicit a psychological trauma preceding the onset of the symptoms and as in peptic ulcer, this trauma may initiate as well as activate a colitis.

In essential hypertension the positive characteristics of the patient are not easy

to define. Such a patient may best be described as the antithesis to the child in mental makeup. He does not play; he has no make believe. He lives a crowded and compact existence. There is no doubt that these traits are largely the result of insecurity, and so, unlike a child, he lives in the future and not in the immediate present. He doesn't play because this may divert his strivings to acquire future security. As a consequence, his mental range is usually narrow, but within this range it is terribly intense. In individuals with essential hypertension one cannot as a rule elicit a history of its having arisen after a sudden psychological trauma. Their whole aspect of life may be regarded as a psychological trauma, and for this reason hypertension is nearly always insidious in onset and slow in development.

Obviously all cases of essential hypertension are not psychogenic in origin. Some are due to obesity, to Cushing's disease, to pheochromocytoma, to lead poisoning and some, although rarely, to unilateral renal diseases. Psychiatrists often overlook this fact.

The personality patterns of other maladies, conventionally regarded as of psychosomatic origin, such as cardiospasm, mucous colitis, anorexia nervosa, neurodermatitis, and possibly certain cases of glaucoma have not yet been sufficiently elucidated. In manic depressive psychosis, the individual always revealed a wide range between elation and depression in his emotional reactions long before the psychosis became manifest. In paranoia, the person was always suspicious, eccentric and afflicted with profound obsessions. Those who are better qualified in psychiatry than I, tell me that these traits date back to childhood.

It may be that in the future these psychological patterns in psychosomatic disease will be more clearly demarcated by finer methods of approach; for instance, by the different disciplines of psychoanalysis. Thus far, however, the largest contribution the Freudian psychoanalysts have made to the study of psychosomatic disease has been in the unraveling of psychological mechanisms whereby these types of personality have developed. Occasionally a successful therapeutics has been obtained. Their efforts have unquestionably been valuable, but if I may be bold enough to venture a criticism, I would say that they would contribute more to the study of psychosomatic diseases by devoting more effort to direct clinical observation than by exercises in semantics and symbolism.

The overlapping of many of the components of these patterns helps to explain the not uncommon association of two or more psychosomatic diseases in the same individual. Essential hypertension and peptic ulcer, hypertension and Graves' syndrome, Graves' syndrome and peptic ulcer, manic depressive psychoses with Graves' syndrome, peptic ulcer and paranoia are not infrequently associated. The combinations are numerous. Curiously, peptic ulcer and non-specific ulcerative colitis rarely are associated. The reason probably is that the two personality patterns are more or less antagonistic.

Only a rabid psychosomaticist would insist that the impact of a persistent emotional situation upon a certain temperament is the whole story in the creation of such diseases. Most of us can think of individuals who conform to one of these types and who have not acquired their own particular psychosomatic disease.



Obviously, there must be other mechanisms that we are as yet unaware of, chemical, physical, endocrine, humoral, etc. We must also consider that psychosomatic diseases possess a long life cycle and that the incubation period may be one of many years. It has been my privilege to have witnessed this transition. Moreover, the powers of adjustment to emotional stress are not always constant. Compensatory mechanisms are always around the corner. One of the largest problems in psychosomatic medicine is the bridging of the wide chasm between the psyche and the soma. Clinically, if we are lucky, we can sometimes observe transitions in some of these psychosomatic disorders. For example, witness the catastrophic clinical changes between essential hypertension and the terminal cardiovascular disease. In Graves' syndrome, one can often note the transition from the larval phase, call it autonomic imbalance, Basedowid, formes frustes, neurocirculatory asthenia or what you will, to the fully blown form with the classical quadrad of signs and symptoms. Although the earliest phase of peptic ulcer is in all probability gastric hypersecretion, we are at present unable to witness transition to ulcer formation, because with the diagnostic methods at our command, the presence of the ulcer can only be determined after it has fully developed. The observation of the intervening phase may come through serial gastroscopy. However, the experimental creation of a peptic ulcer, especially by the method of Mann and Williamson (6) affords a clue as to what we may expect to find in the human being. In non-specific ulcerative colitis we are entirely ignorant of the earliest phases. It would be intriguing if the earliest phase were mucous colitis but clinical facts are as yet insufficient to warrant such a statement. But there are a number of observations that lead us to believe that the larval form is an irritable or spastic colon. The initial phases of the other psychosomatic diseases that we have mentioned appear to be only mild expressions of the mature types and they have not been endowed in the past with a different nosological status.

The psychosomatic diseases thus lend themselves especially to study from the biological rather than the static viewpoint, an aspect that is missing in much of the current psychosomatic literature. It is to be regretted that much of the activity in psychosomatic medicine is mostly in the hands of pure psychiatrists. The converse is equally true; greater progress would come if the clinician were a better psychiatrist. In fact, many are not even receptive to the ideas underlying psychosomatic medicine.

Even if we knew more completely the clinical biology of these disorders, we would still be far from understanding the nature of the abnormal physiological responses kindled by their impact, their sequences, their interrelations and especially the manner whereby these physiological responses are converted into gross morphological changes. A vast host of mechanisms are set into play. There can be little doubt that many of the physiological changes are mediated through the autonomic nervous system and the hypothalamus, and the experimental work on stimulation or the abolishing of the activity of these centres has enlarged our knowledge appreciably. Cannon's work, especially, has far reaching implications, and he has emphasized the teleological or emergency nature of these reactions. Unfortunately, our methods of approach are still



crude and the interrelation between the autonomic, the somatic nervous system and the endocrine organisms are so close and so complex that it is difficult to isolate the reactions between the various systems. Unfortunately, the autonomic nervous system has been the victim of infinitely more speculation than of experiment. The autonomic nervous system is continually invoked as the "cause" of this or that psychosomatic disease. This has made sterile much of the work on the etiology of the psychosomatic diseases. The autonomic nervous system may be the mechanism whereby the physiological responses are mediated, and this, of course, is well worth knowing, but the determination of such a mechanism is by no means synonymous with "cause." Causality in disease constitutes a chain of circumstances and events and is never a single and isolated factor.

One can now grasp why the average conventional hospital history of a psychosomatic disease is woefully incomplete. Such histories only begin when the clinical manifestations have become apparent. But the malady began long before, sometimes even from birth. An adequate history of psychosomatic disease should therefore include a panoramic survey of the patient's entire life history, his reactions to the members of his family, his social and economic status, his loves, his fears, his strivings, his hates. Such tridimensional histories need not necessarily be recounted in psychoanalytic detail; in most instances, gross data and not the microscopic details usually suffice. In view of the prevailing increase in the psychosomatic diseases, not to speak of the neuroses, the hospital of the future will be manned by a much larger body of psychiatrists than at present. A better solution would be to convert internists into psychiatrists.

Experimental investigations are handicapped by the fact that psychosomatic diseases are essentially human diseases; experimental methods to reproduce them have therefore largely failed because they cannot introduce the human equation. The only psychosomatic disease which has been successfully reproduced experimentally is peptic ulcer and this only by methods that are totally unphysiological for man. By the same token, lower animals are practically immune from the psychosomatic diseases.

Curiously, in all but one of the psychosomatic disorders there is a common variety of physiological response, namely an exaggeration of one or more normal functions. In essential hypertension it is the intravascular pressure; in Graves' syndrome the basal metabolic rate; in peptic ulcer, the gastric secretion; in ulcerative colitis, the tonicity, peristalsis and the intestinal secretions; in cardio-spasm, the tonicity of the cardiac sphincter. This exaggeration applies as well to some of the psychoses; in manic depressive insanity, there is an exaggeration of the normal emotional rhythm between elation and depression. In paranoia, there is exaggeration of the normal affective state of mind. This concept may apply to certain forms of schizophrenia, but I am not sure. This exaggeration of one function is the dominant evidence of the disease, although an exaggeration of other normal functions in varying degrees of activity may partake in the clinical expression. I have employed the term *hyperkinesis* (7) to this process. One may construct the following biological sequence. Constitution + psychological trauma  $\rightarrow$  hyperkinesis  $\rightarrow$  somatic disease.

The only psychosomatic disease in which exaggeration does not apply is

anorexia nervosa. This malady is characterized by a depression of a wide range of functions; the basal metabolic rate, the body temperature, the estrogenic function, the blood pressure and the gastrointestinal muscular activity and its secretions. Why this psychosomatic malady should behave contrariwise to the other psychosomatic diseases is a mystery.

The hyperkinesis or hypokinesis in all these aforementioned disorders indicates that the search for a specific test will probably fail, because the transition from the normal or static phase to the abnormal or dynamic phase is subtle and the line of demarcation is an indefinite one. All bodily functions have ranges within a normal, not an exact mathematical quantity. The diagnosis of these diseases, therefore, depends upon a perspective of the composite picture in which a study of the personality and life history of the individual is a vital consideration.

Why does one person get hypertension, the second peptic ulcer, the third Graves' disease and so on? This is one of the important issues in psychosomatic medicine. The easiest solution would be to invoke the doctrine of "organ inferiority." This is purely hypothetical and I know of no evidence that justifies such a doctrine. The answer probably lies in the manner in which the individual reacts to emotion. I have already mentioned that one person vomits, the second trembles, the third moves his bowels, the fourth gets palpitation, the fifth flushes, the sixth feels a lump in the pit of his stomach, the seventh acquires a rise in blood pressure, etc. Usually, two or more of these reactions arise simultaneously. It is not difficult to conceive that these reactions which represent exaggerations of normal function may become fixed, provided the emotion is powerful enough and is experienced over a prolonged period. Alfred Cohn (8) reported an interesting observation in World War I. During his inspection of base hospitals in the week after the armistice, he found only rare instances of neurocirculatory asthenia, whereas previously they had been common. That this concept has some validity is reflected in some psychosomatic diseases in which clinical transitions may be readily observed. In the early phases of hypertensive disease, the hypertension is labile, in the later phases it is fixed. In manic-depressive insanity and in paranoia, lability of the symptoms in the early phases is followed by fixation. In Graves' syndrome, when one has the opportunity to note the development of the disease in someone whom he has known well, the same sequence of events is noted. It is apparent that in the hyperkinesis of a psychosomatic disease, there are 5 phases. 1. Constitution. 2. The exaggeration of a normal function. 3. Lability of the exaggerated function. 4. Fixation. 5. Somatic changes. It is in the transition between 4 and 5, that is, the elucidation of the mechanisms whereby fixed exaggerated functions results in organic changes, sometimes sufficient even to kill, that one of the main problems in psychosomatic medicine lies.

A much abused expression in the medical writings is the word "unknown" when applied to the causation of the psychosomatic disease. This does not represent modesty on the part of the authors but indicates rather a mechanical turn of mind. For such writers, anything that cannot be tested in a test tube, a blood counting apparatus or an electrocardiogram, does not exist. It is a fact that we

do not know the cause of any disease fully; at most, we are aware of part of the chain of circumstances that bring it about. In psychosomatic diseases we see at least a small part of the chain, but to give a blanket indictment that the cause of a disease is not known because we do not know the entire chain is misleading.

Inasmuch as the human equation always enters into their production, the psychosomatic diseases are essentially diseases of the higher civilizations. Furthermore, evidence is strong that they are increasing, and the prospect is good that they will continue to increase unless social, economic and political insecurity is remedied. Attempt at prophylaxis, I need hardly add, is therefore not encouraging. In the meantime, much can be done by adjustment of the individual with the aid of the many forms of psychotherapy that are available. Unfortunately, psychotherapy has enormous limitations. It is painstaking, time consuming, and expensive, and a large percentage of the afflicted have insufficient culture or intelligence to comprehend it. Above all, psychotherapy is of little avail in the fixed and especially in the somatic phases. In these phases, surgery has done much by methods that reduce the exaggerated function to a lower level. In only one of the psychosomatic diseases can a normal function be completely removed, namely peptic ulcer, and a lasting cure be attained. In the remainder, only a reduction of the exaggerated function to normal levels can be accomplished, a milieu that is still potential for a recurrence. That is why, in psychosomatic disease, management only begins when the operation is finished.

In this sketchy survey I have acted the part both of an attorney for the defense and the prosecutor. It is with some misgivings that I now assume the part of a judge; to give a verdict upon the future of psychosomatic medicine and to suggest a discipline of study whereby it may become a worthy member in the hierarchy of specialties in medicine. Psychosomatic medicine no longer needs an apology; it has long passed that stage. But a discipline is needed so that it will grow strong and lusty and above all that it be protected from its overzealous advocates. I shall therefore make a few suggestions. 1. The greatest need is a wider awareness of the principles and implications of psychosomatic medicine; one does not ask that you believe in it but that you shall be willing to believe. This awareness is essential not so much for the better orientation in a wide variety of diseases that are increasing but rather because it will help create a larger student body than the present handful. Psychosomatic medicine needs internists as well as psychiatrists, and no matter what new blood enters the field that training must be bivalent. When Sydenham was asked by a student to recommend the best book from which to train himself in the practice of medicine, Sydenham replied, "read 'Don Quixote.'" 2. Psychosomatic medicine requires more clinical observation and less dialectic. Repeating words and formulas smacks of Galenic medicine. By observation we do not refer to the mere attainment of a snapshot picture but to a moving picture film of disease; in other words, a biological approach. We would not know that the frog was once a tadpole unless we saw the transformation. 3. The bridging of the transition between the psyche and the soma. This is the most difficult job of all, because the lower animals are not subject to the psychosomatic diseases. Nevertheless, in man, quantitative

methods of measuring different varieties of emotion are possible, and may help in partially bridging the gap. From this point to the initiation of the somatic lesion will require studies on the physiology of the autonomic nervous system by new methods of approach. The discovery of the chemical transmission of nerve impulses, it seems to me, fore-shadows such an event perhaps with a study of the finer shades of cellular pathology. Electroencephalography in the study of emotions is still a comparatively untitled field.

I close with the hope that this discourse may help in the promotion of an aspiration that is in the minds of nearly all of us, namely that in hospitals people should be treated and not diseases.

#### BIBLIOGRAPHY

1. FREUD: quoted by Stanley Cobb: *Borderlands of Psychiatry*, Cambridge, Mass., Harvard University Press, 1943.
2. CANNON: *Bodily Changes in pain, hunger, fear and rage*, New York, D. Appleton & Co., 1915.
3. WOLFF AND WOLF: *Human Gastric Function*, New York, Oxford University Press, 1943.
4. HOELZEL: *Am. J. Digest. Dis.* 60: 188, 1942.
5. FRIEDMAN AND KASSANIN: *Arch. Int. Med.*, 72: 767, 1943.
6. MANN AND WILLIAMSON: *Ann. Surg.* 77: 409, 1923.
7. MOSCHCOWITZ: *Am. J. M. Sc.*, 206: 576, 1943.
8. COHN: *Arch. Int. Med.*, 158: 453, 1919.

## LIFE'S LATER YEARS

### STUDIES IN THE MEDICAL HISTORY OF OLD AGE

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#### PART 10<sup>1</sup>

#### THE EIGHTEENTH CENTURY

*"But grant, the virtues of a temp'rate prime  
Bless with an age exempt from scorn or crime;  
An age that melts with unperceived decay,  
And glides in modest Innocence away;  
Whose peaceful day Benevolence endears,  
Whose night congratulating Conscience cheers,  
The gen'ral fav'rite as the gen'ral friend:  
Such age there is, and who shall wish its end?"*

*Samuel Johnson—The Vanity of Human Wishes.*

Although Garrison has characterized the Eighteenth Century as the "Age of Theories and Systems," and has described much of its thinking as "tedious and platitudinous philosophizing," we shall nevertheless find substantial achievements in the field of old age, such as the progress in pathological and clinical correlations, the increasing understanding of cardiac pathology, physiology and therapy, the rise of scientific surgery and dentistry, advances in ophthalmology and cerebral physiology, and finally an outstanding contribution to physical diagnosis (1). In addition we record the publication in 1724 of Sir John Floyer's *Medicina Gerocomica*, the first English work on old age (2), and in 1754 of Johann Bernhard von Fischer's pioneer book, *De senio eiusque gradibus et morbis* (3), in which the foundations were laid for the scientific approach to the problems of senescence and of disease in the aged.

Although the celebrated supercentenarian Thomas Parr died in 1635, Harvey's description of the post-mortem examination was not published until 1669, nine years after the death of the great physiologist (4). The influence of this classic necropsy was widespread and from time to time other post-mortem observations on the very old found their way into medical literature. In 1699 the French anatomist and surgeon, François Poupart (1616-1708) described the occurrence in a man aged 100 years, of marked spinal ankylosis, involving the nine lower vertebrae and characterized by extensive new bone formation (5). Dr. James Keill of Northampton, England, reported in 1706, "An Account of the Death and Dissection of John Bayles, of Northampton, Reputed to Have Been 130 Years Old" (6).

<sup>1</sup> This is the tenth in a series of articles dealing with Studies in the Medical History of Old Age. Upon completion of their publication, the installments will be collected and reprinted in a single volume, constituting one of the Series of Monographs of The Mount Sinai Hospital Press.—Ed.



In this paper Keill discussed his patient's habits, the evidence for his alleged age, and then described in detail his findings at the autopsy, comparing them frequently with those observed in Parr. He ascribed the fatal outcome to the weakness of Bayles' stomach, and to the hardness and dilatation of the aorta. In this connection, the keen physician, a worthy student of Harvey, made the following observation:

*"...and it was impossible that his blood could circulate duly while the great artery, having lost its elasticity, by being become cartilaginous, could give no motion to the blood: it is very probable that this was the cause of his irregular and intermittent pulse which I have felt some years before he died."*



FIG. 1. Sir John Floyer (1649-1734). A line drawing, found in a volume in the Bodleian Library, said to be the only known portrait of Floyer.

This may well be the first description of the irregular pulse of auricular fibrillation in which the causative factor of arteriosclerosis was demonstrated post-mortem. Keil believed that both Parr and Bayles owed their longevity to the strength of their hearts, the large size of their chests and the good quality of their lungs.

Scheuchzer, a Swiss physician and naturalist (1672-1733) published the clinical history and post-mortem findings in a man aged 109 years and 3 months. Here also the emphasis is laid on the marked arteriosclerosis, the aneurysmal dilatation of the aorta and the cartilaginous thickening of the aortic valve (7). Haller, the great physiologist, to whom we shall return later, recorded in 1747 the findings in a female centenarian (8). Cheselden (1688-1752) the renowned English surgeon, in his "Anatomy of the Human Body," first published in London in 1712, discussed the large size of the aorta in two men, each past the century mark and in one woman also of advanced age (9).

These isolated reports on the pathology of the aged indicate the widespread interest in the organic basis of disease that later found its highest expression in

the work of Morgagni and Baillie. Before proceeding to these great figures we must break off to discuss other aspects of the medical interest in our theme, much of which, although of purely historical interest, serves nevertheless to round out the medical and social background of the period.

The unusual ability of Sir John Floyer (1649-1734) was first shown in his "Treatise on Asthma," published in 1698, which ascribes the disease to a "contraction of the bronchia" (10). In this work the post-mortem examination of a case of pulmonary emphysema was presented. He was an ardent advocate of the cold bath as a health promoting agent and advised its use in the treatment of disease. These views were set forth in "An Inquiry into the Right Use of the Hot, Cold and Temperature Baths in England" (11). Floyer was the first after Cusanus and Sanctorius to count the pulse (12) and is reputed to have been the earliest advocate of the use of mineral oil in constipation. Young Samuel Johnson's trip to London to be touched by Queen Anne for the "King's evil" was undertaken on Floyer's advice.

The *Medicina Gerocomica* or the "Galenic Art of Preserving Old Men's Healths," (1724) emphasized that old people are afflicted by characteristic forms of illness, which vary according to the individual constitution (13). For each type a different therapy is needed. Although his book is based on Galen, and all disease is ascribed to the *cacochymia*, or bad composition of the body fluids, Floyer's opinions are based on personal observations.

*"Autumn and Winter are most injurious to old Men, whose Heat is weak, and the Circulation and the pulses are most stopt. In Spring and Summer they are the most healthful. . . The florid and fat old men then are of a sanguine Constitution, and preserve that Temper, by avoiding all Excesses in the hot and cold Regimen. They are most healthful, and I reckon them in the middle of the acrid, chloeric, and salt tempers, which abound in the thin, hot old Men; and the pituitous and serous Humors and Slime, which appear in the cold, fat, pale, old Men."* (12)

A contemporary of Floyer, George Cheyne (1671-1743) enjoyed the friendship of great physicians and of Samuel Richardson, the novelist. His popular reputation was large, in spite of the fact that he "preached temperance to an intemperate generation" (13). He was an extreme vegetarian; his own diet as well as that prescribed for his patients was chiefly vegetables and eggs. His views on diet and health were based on his personal experience, since his early excesses forced him to reform his way of life and to reduce his weight radically. His "Essay of Health and Long Life" achieved great popularity and ran to many editions, the 6th appearing in 1725 (14). The following paragraph is typical of Cheyne's viewpoint.

*"...since 'tis certain aged Persons become Children, as to the weakness of their Digestions, they ought to diminish, as Children increase in their Food, from weaker to weaker, and from less to less. For as their Solids are unelastic, their concoctive Powders weak, their Perspiration little, and the Ex-*

*penses of living scarce any, their Repairs (not to overlay the Spark of Life remaining) ought to lessen proportionally. And 'tis to the Neglect of this, in aged Persons that those Rheums, Catarrhs, Winds and Colicks, Loss of Memory and Senses, their Aches and Pains, and all that dismal and black Train of Miseries that wait on Long Life, is mostly owing. Which by a discreet and timeous lessening of their Diet, might, in a great measure be prevented."*

Cheyne's book "The English Malady," was concerned with nervous diseases, spleen, vapors, and lowness of spirits, and contains much autobiographical material (15).



FIG. 2. George Cheyne (1671-1743)

Still another work on the hygiene of old age, *De Aetate Vergente Liber* (16), was published in 1724 by Dr. Robert Welsted (1671-1735). The author, holder of degrees from Oxford and Fellow of the Royal Society, was an industrious writer on medical and scholarly topics, but in this work is content to reiterate the admonitions against overeating and excessive drinking that Galen and the Arab physicians had impressed so deeply on medical thinking many hundreds of years before.

The celebrated Richard Meade (1673-1754), who inherited from Radcliffe

the famous gold-headed cane, discussed old age in his *Monita et Precepta Medica* (1751) in the form of opinions whose source is likewise obvious.

*"The frigidity of men advanced in years is a faithful monitor that points out to them the folly of forcing themselves to exert a vigor which they have lost, vainly expecting raptures, but finding only irksome labor which will shorten their days."*(17)

Meade's *Medica Sacra* or "A Commentary on the most remarkable Diseases mentioned in the Holy Scriptures," appeared in 1749 when he was in his 77th year, and in the preface he stated that the book resulted from his efforts "to pass his leisure pleasantly for himself and not useless for others." In Chapter VI, entitled the "Disease of Old Age," we find an ingenious interpretation of the famous twelfth chapter of Ecclesiastes. In an interesting essay, the late Sir Humphrey Rolleston compared Meade's version of these lines with that of many other commentators (18).

The earnest bibliographer in the field of old age will eventually encounter a reference to Dr. John Hill's "The Old Man's Guide to Health and Long Life" (19). Lest any time be wasted on this worthy, who also wrote "On the Virtues of Sage in Lengthening Human Life, with Rules to attain a Long Life" (20), we quote the summation of Hill's character to be found in the Dictionary of National Biography: "a versatile man of unscrupulous character, with considerable abilities, great perseverance and unlimited impudence" (21).

In the works of the great Dutch clinician and teacher, Hermann Boerhaave (1668-1738), there are only occasional references to old age as a medical problem. In the English translation of his famous aphorisms, we find in No. 1015 the following: "The greatness of an Apoplexy is therefore measured by the Age, Constitution and Make-up of the Patient" (22). In the commentary of the English translator on the aphorism devoted to urethral stone, we find a fascinating clinical recital, with a most unusual course and a happy ending.

*"About ten years ago I was called to the late Sir William Langhorn, at Charleton in Kent, then aged Eighty-one, who had made no water for above thirty-six Hours. Whilst I sent an Express away to the late Dr. Cyprianus, I endeavored by all possible means to remove the stone out of the urethra; but finding it impossible, and that the old Knight was in a Lethargy, and all his lower Belly and Genitals burning hot, I sent in haste for the nearest Surgeon. We cut through the Penis longways into the Urethra, and let out the Stone; upon which the Urine flow'd abundantly, and he recovered well enough so as about three years afterward to be married to a young Girl of Fourteen; and, as they say, to consummate the Marriage. The Wound was cured in a few days with Unguentum Apostolorum."*(23)

Gerhard van Swieten (1700-1772), Boerhaave's most famous disciple, is noted as the founder of clinical instruction in Vienna, where he taught for many years. He introduced the use of mercuric chloride in the treatment of syphilis, and is

remembered for his works on military medicine and for his commentaries on Boerhaave's aphorisms. In his *De senum Valetudine tuenda*, an address given at a university celebration, he recognized the age changes in the blood vessels and described shrinkage of the intervertebral discs, but at the same time repeated Galen's dicta on the dryness and coldness of the aging body. His hygienic and dietetic advice is entirely based on Galen, but he attacked such remedies for a long life as the heartbone of the deer and the flesh of mummies. He is pessimistic about the value of treatment in old people (24).

Among Boerhaave's students may also be reckoned Johann Heinrich Cohausen (1665-1750) who after extensive studies at the universities of Leyden, Amsterdam and probably Bordeaux, settled in Coesfeld, the summer residence of the Lord Bishop of Munster. Here, in 1699, he attracted the attention of the court by his book *Tentaminum physico-medicorum curiosa de vita humana theoretice et practice per Pharmaciam prolonganda Decas*, a learned review of all the efforts of mankind to lengthen life and to find means against death and disease (25). This early work is of significance only as it makes clear that the subject of longevity was a life-long interest of Cohausen, for in 1740, he wrote "*Hermippus Redivivus*" (26), which was based on a Roman tomb inscription, ascribing the advanced age, 114 years, of the deceased Hermippus to inhaling the breath of young girls. Cohausen with deliberate humor, conjures up a picture of the old Roman as a teacher in a young ladies seminary, and from there goes on to discuss David and Abishag as well as other instances in history and literature, both ancient and more recent, where odors and other sensations of many kinds seemed to refresh and comfort. Cohausen's concluding words made his purpose clear. "That I at my age should spend my time with the girls, no matter how properly god-like, neither my love of life nor my fear of death would bring me. At all events let no one take as serious medical advice that I have presented here about the exhalations and expirations of young women, but it is to be looked upon only as the last exercise of an old man to bring out that nothing is so improbable that it cannot be explained neatly and deceive the credulous with the appearance of truth, even stimulate them to imitation in hope of a long life." The book in spite of the author's avowal that it was "the recreation of an old man" was received with great seriousness and translated into several languages. The English version by the Scottish scholar, John Campbell, appeared in 1743 and was reprinted in 1749 with many additions by the translator. Of Campbell's version of Hermippus, Dr. Johnson pronounced the volume "very entertaining as an account of the hermetic philosophy and as furnishing a curious history of the extravagancies of the human mind; adding, "if it were merely imaginary it would be nothing at all" (27).

To Johann Bernhard von Fischer (1685-1772) goes the credit for the first medical work on old age to break away from medieval tradition and to attempt an approach to the problem in the modern spirit. His *De senio eiusque gradibus et morbis* (3), first published at Erfurt in 1754, vigorously attacked the prevailing medical pessimism about the aged, and emphasized in his introduction that he would prove the efficacy of therapy with actual cases. The author was personal physician to the Empress Anna Ivanovna and general director of Russian medi-



cal institutions. He was an active administrator, encouraging the foundation of new medical schools, and the preparation of texts to be used in the instruction of students. He served in Russia with great distinction from 1734 to 1742, and then returned to the practice of medicine in Riga, his birthplace.

The first part of the book Fischer devotes to the anatomy and physiology of old age, undertaking to differentiate normal and pathological aging and stressing the need for post-mortems to clarify these problems. His judgment is based on his own necropsies. As characteristic accompaniments of old age he lists the dilatation of the heart and aorta, the calcification of the smaller vessels, the firmness of the brain and the hardness of the glands, the absence of changes in



FIG. 3. Giovanni Battista Morgagni (1681-1771)

the lungs, the cartilaginous thickening of the splenic capsule, and the degeneration of the bones. He describes the characteristics of the respiration, pulse, sleep, nutrition and excretion. The second chapter is devoted to the diseases and their treatment. In the third he gives general rules of hygiene to be followed by the old. Steudel points out that to evaluate Fischer's work properly one must realize that it antedated Morgagni's *De sedibus et causis morborum* by seven years and that volume eight of Haller's *Elementa physiologiae corporis humani*, in which old age was discussed, did not appear until 1766. Von Fischer seems therefore to deserve consideration as the real pioneer of our present day attitudes, rather than Canstatt to whose book, first published in 1839, this honor has often been accorded in the past (28).

The famous Swiss physiologist, Albrecht von Haller (1708-1777), noted as a

German poet as well as for his medical contributions, gave evidence of his interest in old age on several occasions. In 1747 he published the post-mortem findings in a woman, aged 100 years (8) in whom were found aneurysmal dilatation of the aorta, stony hard excrescences and thickening of the aortic valves, arteriosclerotic changes in the aorta and its branches, and gall-stones. Haller's idea of the pathogenesis of arteriosclerosis is of great interest, since this publication antedated Scarpa.

*"This. . . shows that the inner lining of the arteries as a result of continually repeated shocks of the heart finally becomes partially hardened, in part becomes torn between the ossified areas that the stem of the aorta is weakened and disposed to aneurysm formation. The autopsy shows that the blood carries with it everywhere true chalk particles, which may not only be deposited in the kidneys, but get caught and accumulate where the finest membranes are torn, and the attraction of chalk particles for rough uneven surfaces is greater than for smoother surfaces."*

This surprisingly well thought out description of both the chemical and mechanical factors in vascular sclerosis is further documented in Haller's "Pathological Observations" (1756) in which the gross changes in senile arteriosclerosis of the aorta are illustrated (29). Finally, in his famous *Elementa physiologiae corporis humani*, published in eight volumes in the years 1757 to 1763, one chapter is devoted to a discussion of the aging process, emphasizing both the physical and the mental changes (30).

*"The rigidity of the whole body, the decrease of the muscular powers, and the diminution of the senses, constitute old age; which sooner, or later, oppresses mortals severely; sooner, if subjected to violent labor, or addicted to pleasure, or fed upon an unwholesome diet; but more slowly, if they have lived quietly and temperately, or if they have removed from a cold to a warm climate."*

Worthy of mention are Albertini (1762-1833), the teacher of Morgagni and a student of cardiac symptomatology and pathology, and de Senac (1693-1770), whose two volume work, *Traite de la structure du coeur, de son action, et de ses maladies* is a landmark in cardiology. In it the author stressed such physical signs of heart disease as dilatation and pulsation of the cervical veins, the pulsations of the cervical arteries, irregular heart action, the appearance of cardiac aneurysm and coronary artery sclerosis (31).

The active interest manifested by physicians both in Great Britain and on the continent in tracing the signs of disease through life and in seeking the explanation after death found its most authoritative and understanding expression in the *De sedibus et causis morborum* of Giovanni Battista Morgagni (1681-1771), published in 1761, when he was himself 79 years old, and embodied the accumulated experience of more than 50 years (32). According to Herrick, "The significance of Morgagni is seen when we realize that he was the efficient proponent of the

method of diagnosing and explaining disease in terms of pathologic anatomy that gradually became more and more prevalent, especially after its adoption by Corvisart and Laennec, a method that for several decades was the one in general use and which to-day still bulks large in the practice of medicine" (33). For the student of old age Morgagni's work is full of examples of the various maladies that afflict the old, as the result of trauma as well as of disease. In the section devoted to apoplexy nearly all the patients are advanced in years. Here we find the celebrated case of the Cardinal Francesco Sanvitalis, aged 55, in whom Morgagni points out that the principal lesion was in the right side of the brain, while the paralysis resulting from it was on the opposite side. Many cases of aortic and cardiac aneurysms are described. Diaphragmatic hernia is divided into congenital and acquired types. Cholelithiasis and various new growths likewise are noted.

In Great Britain the vivid description of the clinical picture of angina pectoris published in 1768 by William Heberden the Elder (1710-1801) stimulated others to seek the cause of this striking symptom complex. John Fothergill (1712-1783) had post-mortems done on two of his patients with angina. In the necropsy on the second patient, a man aged 63 years, performed by John Hunter himself, the heart was "of ligamentous consistence and in many parts of the left ventricle almost white and hard. . . . The two coronary arteries from their origin to many of their ramifications upon the heart were become one piece of bone" (34). The association of angina pectoris and coronary disease was well known to Edward Jenner (1749-1823) of smallpox fame and Caleb Hillier Parry (1755-1822) of thyrotoxicosis renown, who predicted the vascular changes ante-mortem in the case of John Hunter himself, and proved the point at his death in 1793. This striking correlation of clinical manifestations and post-mortem findings was unappreciated and neglected for over 100 years, until, as Dock (35) has traced, the work of many clinicians including Herrick's conclusive contribution (36) finally made evident to physicians that coronary thrombosis occurred commonly and could be diagnosed accurately.

John Fothergill, who was an intelligent, highly successful and well beloved practitioner, re-enters the present narrative by reason of his work, published in 1762, entitled "Rules for the Preservation of Health, containing all that has been recommended by the most eminent Physicians, with the earliest Prescriptions for most Disorders incident to Mankind, through the Four different Periods of Human Life, being the Result of Many Years Practice" (37). This book is distinguished more by good sense than originality. Galen and Welsted are quoted approvingly, and emphasis is laid on the importance of diet, rest and mental calm and cheerfulness, the latter being helped by seeking the society of young people.

In stressing the advances of pathological anatomy, one must not overlook the progress in physiology. The chemical discoveries of Scheele, Priestly, Cavendish, Black and Lavoisier overthrew the old phlogiston theory and established the role of oxygen in respiration and fundamental bodily processes. Stephen Hales (1677-1761) in his *Hemodynamics* was the first to measure blood-pressure

by inserting a glass tube into the carotid artery of a horse. The French school of neurologic surgeons, Du Petit (1664-1771), Lorry (1725-1783) and Saucerotte (1741-1814) made great advances in clarifying the functions of the brain and spinal cord. General surgery and dentistry were elevated to positions of standing in science by the work of John Hunter and his school. The introduction of digitalis by Withering, and his explanation of its proper mode of employment gave physicians a potent remedy in heart failure. Ophthalmology was advanced by the work of Daviel (1696-1762), originator of the modern surgical treatment of cataract, O'Halloran's (1728-1807) contribution to the study of glaucoma, and by Young's (1773-1829) description of astigmatism and the nature of accommodation. Increasing understanding of the structure and function of the ear by Valsalva and Scarpa led to improved methods of treating deafness and other ear disturbances.

In the field of internal medicine relating to the diseases common to old age, we call attention to Wollaston's discovery of urates in gouty joints, and Dobson's proof that the sweetness of the urine and blood serum in diabetes, first noted by Willis, was due to sugar. Rollo advocated and reported great success with a meat diet in diabetes. Of great significance for personal hygiene was the publication of Johann Zacharias Platner's (1694-1747) "*Treatise on Cleanliness*," in which he pointed out that the body reabsorbs the impurities from soiled clothing and that these provide a basis for disease by penetrating the fluids of the body. He also advised frequent change of underwear, and of the bed-linen of the sick (38).

In 1761 Leopold Auenbrugger published his classic "*Inventum novum*," in which he described the method of percussion and its practical application to the diagnosis of chest diseases (39). This remarkable contribution to physical diagnosis was neglected by his contemporaries and might have been entirely forgotten had it not been for Corvisart, the forceful French clinician, who in 1808 took up Auenbrugger's method and gave to it his enthusiastic endorsement. Herrick has recently discussed the reasons for the long neglect of this great medical innovation, pointing out that not the least of the many factors operating was the unpleasant personality of the discoverer himself (40). Auenbrugger's clinical experience in the use of percussion is indicated by his direct reference to its interpretation of the diseases of old age. In discussing the absence of abnormal sounds in certain coughs and asthmas, which he ascribes to irritability of the nerves of the chest, he includes specifically "the nervous consumption and asthma of old persons." Elsewhere in discussing acute cardiac dilatation, where the enlargement of the area of precordial dullness can be demonstrated by percussion, he draws a vivid picture of the patient's appearance shortly before death, and points out that, "in contrast with the young, older persons, indeed, bear more tranquilly their sufferings." These passing references to the peculiarities of the aged serve to remind us once more that, in every period of medical development, contact with the pressing problems of sick old people has been an unavoidable part of every physician's experience.

The continuing stream of popular works on old age, devoted to much the same

topics as were discussed by Galen and the Arab physicians, indicates a sound cumulative realization that old age is to some extent what the individual makes it, and that moderation in all things tends to prevent or at least postpone many of the unpleasant features commonly associated with senescence. Christian Wilhelm Hufeland (1762-1836) was at one time a member of the Weimar group that included Goethe and Schiller. A man of wide interests, of great human sympathy and an enthusiastic medical teacher, he left a deep imprint on German medicine, founding journals and, as professor at Berlin, making important improvements in methods of teaching. His book, entitled *Makrobiotik, oder die Kunst das menschliche Leben zu verlaengern*, appeared in 1796, and was translated into English and all the continental tongues (41). One American edition ap-

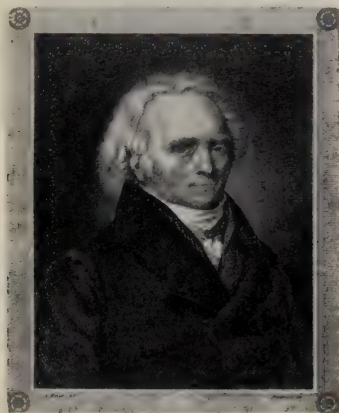


FIG. 4. Christian Wilhelm Hufeland (1762-1836)

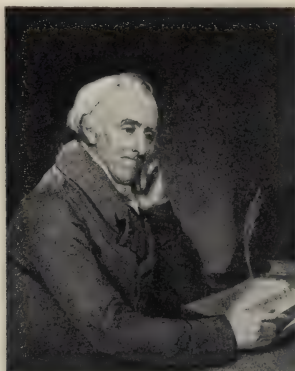
peared as late as 1854. It is a well written work, sympathetic, optimistic and covers a wide field of topics. While in no sense original, its message is expressed in such a delightful way that its popularity is easily understood.

As a result of the persistence of the medieval university organization into the four faculties of theology, philosophy, law and medicine, the only pathway to the natural sciences lay through the study of medicine. The foundations of geology, mineralogy, physics, chemistry and botany were in many cases laid by gifted men trained as physicians. The converse, the contributions of non-medical individuals to medicine, is far less commonly encountered. Easily in the first rank of medical amateurs stands Benjamin Franklin (1706-1790). A study of his broad accomplishments is not in order here, but the reader will recall his substantial additions to the welfare of the elderly, such as the flexible catheter



and the bifocal lens, as well as his studies on the ventilation and heating of houses (42).

Franklin's personal physician was the illustrious Benjamin Rush of Philadelphia (1745–1813), noted not only as a practitioner and teacher, but also for his active participation in politics and his leadership in matters of communal welfare. His writings cover a wide range of medical topics, including insanity and old age. In his work on the diseases of the mind, he does not seem to have recognized any specific type of mental disease in the aged, stating that “there is greater predisposition to madness between twenty and fifty than in any of the previous or subsequent years of human life.” He gives several exceptions to



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FIG. 5. Benjamin Rush (1745–1813)

this rule from his own experience, and attempts in the following quotation to explain the freedom of the aged from acute manic seizures.

*“There are two reasons why this disease so rarely attacks old people. Their blood vessels lose their vibratility from age, and hence, they are less liable to fevers than in middle life; and from the diminution of sensibility in their nerves and brains, the causes of madness make but a feeble and transient impression upon their minds. In the latter condition of their bodies, they revert to that state which takes place in children and which I have said protects them from frequent occurrence of this disease.”* (43)

His “Account of the State of the Body and Mind in Old Age, with observation on its diseases and their remedies” (1793) was the first American contribution

to the subject, and was acclaimed both in this country, in England, and on the continent where it was widely circulated in translation. It is a simple direct little essay, based entirely on the author's own observations and a few authorities, to whom he gives full credit. A noteworthy feature is his reference to many of his distinguished patients by name. Dr. Franklin, we are told, "had two successive vomicas in his lungs before he was 40 years old." "Dr. Franklin informed me, that he recognized his friends after a long absence from them, first by their voices." "Dr. Franklin owed much of the cheerfulness and general vigor of body and mind, which characterized his old age, to his regular use of this remedy (the warm bath)." "An inflammation of the lungs, which terminated in an abscess, deprived the world of Dr. Franklin."

This is a practical work, well worth reading to-day, for its sharp comment and sound observations concerning the physical and mental characteristics of the aged, including such items as the broad gait, the failing memory, the eccentricities of appetite, the dysuria, the emotional disturbances and the lack of a fear of death. The clinical insight of Benjamin Rush into the problems of old age formed the foundation for the further pursuit of knowledge in this extensive field in the New World. In like manner it serves as a fitting conclusion to the accomplishments of one century and as an inspiring introduction to the greatest century of medical achievement yet recorded.

## BIBLIOGRAPHY

- (1) GARRISON, F. F.: *An Introduction to the History of Medicine*, ed. 4, Philadelphia, Saunders, 1929, p. 310.
- (2) FLOYER, SIR J.: *Medicina Gerocomica*, or the galenic art of preserving old men's healths, explain'd in twenty chapters. To which is added an appendix concerning the use of oyls and unction in the prevention and cure of some diseases. As also a method from a Florentine physician of curing convulsions and epilepsies, by external operation. London, J. Isted, 1724.
- (3) VON FISCHER, J. H.: *De senio eiusque gradibus et morbis*. Erfurt, 1754, ed. 2, 1760. German translation, Leipzig, 1777.
- (4) The first publication of Harvey's autopsy on Thomas Parr, was in *De Ortu et Natura Sanguinis*, London, 1669, by Dr. Betts, to whom the manuscript had been presented by Harvey's nephew.
- (5) POUPART, F.: *Hist. de l'acad. royale des sciences*, Annee 1699. Avec les memoires de Mathemat. et de Phys. pour la même annee, p. 50.
- (6) KEILL, J.: *Phil. Trans. Royal Society*, 25: 306, 2247, 1706. Abridged, vol. 5, (1703-1712), London, 1809.
- (7) SCHEUCHZER, J. J.: *Acta Vratislaviensa*, p. 189, 1724. See also *Phil. Trans. Royal Society*, 376: 313, March, 1723.
- (8) HALLER, A.: *Observationes duae fabricae morbosae in cadaveribus repertae*. *Phil. Trans. Royal Society*, 44: 483, 528, 1747.
- (9) CHESelden, W.: *The Anatomy of the Human Body*, London, 1713. The 13th ed. appeared in 1792.
- (10) FLOYER, SIR J.: *A Treatise of the Asthma*, divided into four parts. In the first is given a history of the fits and symptoms preceding them; in the second, the cacochymia, which disposes to the fit, and the rarefaction of the spirits which produces it are described; in the third the accidental causes of the fit are observed; in the fourth the cure of the asthma fits and the method of preventing it is propos'd. ed. 2, London, R. Wilkins & W. & J. Innys, 1717.

- (11) FLOYER, SIR J.: The ancient  $\Psi\text{TX}\rho\text{O}\text{A}\text{O}\text{T}\Sigma\text{I}\text{A}$  revived, or an essay to prove cold bathing both safe and useful. In four letters, London, S. Smith and B. Walford, 1702.
- (12) FLOYER, SIR J.: The Physician's Pulse Watch, London, S. Smith and B. Walford, 1707.
- (13) CHEYNE, G.: An Essay of Health and Long Life, London, G. Strahan, 1724.
- (14) CHEYNE, G.: Article in Dictionary of National Biography, London, H. Milford, 1917, vol. 9.
- (15) CHEYNE, G.: The English Malady, or a treatise of nervous diseases of all kinds, as spleen, vapours, lowness of spirits, hypochondriacal and hysterical distempers, etc., London, S. Powell, G. Risk, G. Ewing & W. Smith, 1733.
- (16) WELSTED, R.: De Aetate Vergente Liber, London, 1724.
- (17) MEADE, R.: Monita et precepta medica, London, J. Brindley, 1751.
- (18) ROLLESTON, SIR, H. D.: Medical Aspects of Old Age, London, Macmillan, 1932. See Chap. 7—The description of old age in the twelfth chapter of Ecclesiastes.
- (19) HILL, J.: The Old Man's Guide to Health and Long Life, London, 1761.
- (20) HILL, J.: On the Virtues of Sage in Lengthening Human Life. With Rules to attain old Age, London, 1763.
- (21) Dictionary of National Biography, London, H. Milford, 1917, vol. 9, p. 848.
- (22) BOERHAAVE, H.: Aphorisms Concerning the Knowledge and Cure of Diseases. From the last edition printed in Latin at Leyden, 1728, with useful observations and explanations, London, 1742.
- (23) BOERHAAVE, H.: op. cit., aphorism 1440.
- (24) STEUDEL, J.: Zur Geschichte der Lehre von den Greisenkrankheiten. Sudhoff's Archiv. f. Geschichte d. Med. u. Naturwiss., 35: 1, 27, 1942.
- (25) COHAUSEN, J. H.: Tentaminum physico-medicorum curiosa de vita humana theoretice et practice per Pharmaciam prolonganda decas. Coesfeld, 1699.
- (26) COHAUSEN, J. H.: Hermippus Redivivus, or the sage's triumph over the grave, London, 1744.
- (27) For additional material on this writer see following:  
     BEAUVOIS, A.: Un praticien allemand au xviiieme siecle. Jean-Henri Cohausen, 1665-1750, Paris, 1900.  
     PAAL, H.: Johan Heinrich Cohausen, 1665-1750, Leben u. Schriften eines bedeutenden Arztes aus der Blutezeit des Hochstiftes Muenster, mit Kulturhistorischen Betrachtungen, Jena, Fischer, 1931.
- (28) For further information on von Fischer, see the following:  
     RICHTER, W. M.: Geschichte der Medizin in Russland, Moscow, 1813-17, Vol. 3, p. 270-79.  
     Biographisches Lexicon, Berlin, Urban u. Schwarzenburg, 1932, vol. 2, p. 225.
- (29) HALLER, A.: Pathological Observations, chiefly from the dissections of morbid bodies, London, D. Wilson and T. Darham, 1756.
- (30) HALLER, A.: Elementa physiologiae corporis humani. 8 vols., Lausanne, vol. 1-5, 1757-1763. Vols. 6-8, Berne, 1764-66.
- (31) DE SENAC, J. B.: Traité de la structure du cœur, de son action et de ses maladies. 2 vols., Paris, J. Vincent, 1749.
- (32) MORGAGNI, G. B.: De sedibus et causis morborum, Venice, 1761.
- (33) HERRICK, J. B.: A Short History of Cardiology, Springfield, Thomas, 1942.
- (34) FOTHERGILL, J.: Works with Life and Notes by John Elliott, London, 1781. Angina cases, pp. 508 and 529.
- (35) DOCK, G.: Historical Notes on Coronary Occlusion, from Heberden to Osler, J. A. M. A., 113: 563-568, 1939.
- (36) HERRICK, J. B.: Clinical Features of Sudden Occlusion of the Coronary Artery, J. A. M. A., 59: 2015-2020, 1912.
- (37) FOTHERGILL, J.: Rules for the Preservation of Health, London, M. Thrush, 1762.
- (38) JENNY, J. J.: Problems of Clothing Hygiene, Ciba Symposia, 6: 1978-1984, 1944.

- (39) On Percussion of the Chest, Being a Translation of Auenbrugger's Original Treatise, entitled "*inventum novum ex percussione thoracis humani, ut signo interni pectoris morbos detegendi.*" (Vienna, 1761) Baltimore, the Johns Hopkins Press, 1936.
- (40) HERRICK, J. B.: A Note Concerning the Long Neglect of Auenbrugger's "*Inventum Novum,*" Arch. Int. Med., 71: 741-748, 1943.
- (41) HUFELAND, C. W.: *Die Kunst das Menschliche Leben zu Verlaengern*, Jena, 1797.
- (42) FRANKLIN, B.: The writings of, edited by Albert Henry Smythe, New York, Macmillan, 1907.
- (43) RUSH, B.: *Medical Inquiries and Observations upon the Diseases of the Mind*, ed. 3, Philadelphia, Grigg, 1827.
- (44) RUSH, B.: An Account of the State of Body and Mind in Old Age, with observations on its diseases and their remedies. In "*Medical Inquiries and Observations,*" Philadelphia, 1793, vol. 2.

## **Dr. Hiram N. Vineberg**

Dr. Hiram N. Vineberg died quietly in his sleep on May 4th, 1945. His passing closed the career of a pioneer gynecologist and one of the most colorful personalities of the medical profession.

There is some uncertainty about his exact age. It was about ninety years ago that he was born on December 20th, in an unknown village near Kovno, Russia. His mother died from a post-partum hemorrhage in giving birth to Hiram and his twin sister.

His father, a lumber merchant, married again soon after the death of Hiram's mother and shortly thereafter, leaving his family behind, he went to Canada. A year later, his wife and children joined him in a little town near Cornwall, Ontario. Hiram worked in his father's store while he attended school.

At the age of fourteen, he ran away from home and engaged in a mercantile business with a cousin. They opened a small country store in the village of Forrester's Falls, Ontario. When he was eighteen, he sold his share of the business for a sum large enough to enable him to take a six month's tutoring course. This permitted him to enter McGill University where he studied medicine for four years. During his course of study at McGill he received the highest scholastic marks that had been recorded for many years and when he graduated in 1878, he won the school's highest honor, "The Holmes Gold Medal."

There is an interesting incident associated with this event. The written examinations at the end of both terms had always taken place on Saturday. At that time, Hiram was a scrupulous observer of the Jewish faith. He explained his situation to the Principal and was granted the privilege of a special examination on Monday. Since that day, the written examinations have been given on Monday instead of Saturday.

Dr. William Osler, who was Dr. Vineberg's professor of medicine at McGill, developed a keen interest in him. This friendship was close and life long. Therefore, when Dr. Vineberg started to practice medicine in Montreal in April, 1878 and his health was poor, on Dr. Osler's advice, he went abroad for post-graduate studies in the Clinics of England. When these studies were completed he accepted an appointment as ship's doctor on the Clipper, "Western Monarch" which sailed for Wellington, New Zealand. At the end of the eighty-nine day voyage, the passengers presented him with a testimonial and thanked him "not only for his qualities as a professional man, but also those of a gentleman."

Dr. Vineberg spent the next year in Hawaii where he was Doctor-in-charge for three sugar plantations on the Island of Oahu. He treated Princess Liliuo Kalini for "Black Tongue" which he recognized as a nutritional deficiency disease. Her father, King Kalakaua, offered him the position as physician of the Leper Colony on Molokai. Although he declined, he visited this place often and became an admirer of Father Damien, whom he described as "the finest man one could possibly meet." When Robert Louis Stevenson wrote his famous "Open Letter to Rev. Dr. Hyde of Honolulu" in vindication of Father Damien



and his work, Mr. Stevenson feared that he might be sued for libel. Dr. Vineberg entered into correspondence with him and offered to go anywhere the libel suit might be brought to testify in Stevenson's behalf.

Returning to Montreal, he located in Portage la Prairie, Ontario, doing general practice. It was during this period that he acquired a liking for Obstetrics and Gynecology, for he said, "Women are more important and worthy of saving than men." To fulfill his ambition to specialize, he spent a year in the Clinics of Berlin, Vienna and Prague.

He returned to New York in January of 1886 and began to limit his work to his chosen specialty. At first he was assistant to Dr. James B. Hunter in the Polyclinic Hospital and then assisted Dr. George M. Edebohls in the Post Graduate Hospital. In 1894 he was appointed Chief of Staff in the Out-Patient Department of The Mount Sinai Hospital. Then in 1910, he was advanced to Associate Attending Gynecologist of The Mount Sinai Hospital and in 1916 to full Attending Gynecologist. He remained in that position until he reached the age of retirement and then became a member of the Consulting Staff.

When he was retired from the Active Attending Staff on March 19, 1921, he was presented with a silver cup and Dr. Solomon Wiener said, "Those of us familiar with your professional career are filled with admiration at the success you have achieved. Coming to New York a stranger to its professional life, you have by your own unaided efforts, won a position of eminence which few of us can hope to equal. It is no exaggeration to say that you have achieved a national reputation. Any word of yours is sure of close and respectful attention in any gathering of the elite of your chosen specialty. In this city your name is a household word in Gynecology."

He finally retired from practice at the age of seventy-five. On being congratulated on this birthday and being asked how it felt to be seventy-five, Dr. Vineberg said, "I remember getting up one morning and saying to my wife, 'I am an old man, I am fifty years old.' I always considered fifty years, old age. Well after I turned seventy," he went on to say, "each day and each month was much profit."

He published over seventy monographs; many on original clinical subjects. They are all written in a simple, yet forceful style; they show evidence of deep study and exceptionally keen clinical insight. Many of his literary contributions have been used and quoted in the best medical text books.

In 1891 at the age of 36, Dr. Vineberg married Lena Bernheim, a cultured, charming woman. She was a loving and devoted wife until her death in 1937. They had no children.

Dr. Vineberg developed pneumonia late in December of 1944. Although he recovered from this acute attack, he showed marked weakness and began to manifest evidence of carcinoma of the stomach. He was fully aware of the nature of his illness but, except to his personal physician, he made no mention of it. Some of his closest friends never suspected this condition as late as a fortnight before his death. Despite his failing health and his increasing feebleness, which friends could not possibly overlook, his spirit was the same. He showed at

all times and up to the very end, that fortitude of which only Saints and heroes are possessed. He did not wish anyone, not even his most intimate friends, to know the nature of his ailment, nor did he wish to see them, as he wanted to spare them, at all costs, the painful awareness of his waning health. His stoicism and courage during his last days were characteristic of his entire life.

On his eighty-fifth birthday, his colleagues brought him out from his retirement. At a gathering held in his honor at The Mount Sinai Hospital, they showered him with praise and presented to him an Anniversary Volume containing scientific contributions by his former associates, pupils and colleagues. His mental alertness at that ripe age is recorded in the published volume which marks an historic event in the annals of The Mount Sinai Hospital, for this honor came to him long after his retirement from active service at Mt. Sinai. Much of the colorful life he led is detailed in that volume. His truly sterling qualities and the important data of his medical career are also included. The student will find it a rewarding task to read the volume dedicated to the life and work of Dr. Hiram N. Vineberg.

We who have had the privilege of close and intimate association with this master miss him more than others. We are grateful for his wise guidance, inspiration and good fellowship. He was indeed a true gentleman and scholar in his professional relationships and a genuine sportsman in the moments of leisure snatched occasionally while off service. Always correct, always fair, fearless in defense of his own rights and in defense of others whom he believed to be right, candid and honest to a fault, it is no wonder he had so many admirers and faithful adherents during his long, useful and exemplary life.

I. C. RUBIN, M.D. AND M. M. PORTIS, M.D.

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Vascular Allergy.* J. HARKAVY. *J. Allergy*, 14:7, November, 1943.

This report deals with fifteen cases suffering from typical bronchial asthma and one in which bronchospasm and cough were the presenting symptoms. Four of the asthmatic patients died and were available for necropsy studies. The chief precipitating factor was considered to be bacterial allergy resulting from chronic sinusal infection. In seven of the sixteen cases, pollen and food hypersensitiveness played additional exciting rôles. The major attacks of asthma were accompanied by inflammatory interstitial lesions in the lungs, sputum eosinophilia, and reactions in serous membranes, characterized by pleural effusions in eight cases, peritoneal exudates in four, and pericardial involvement in three cases. The aspirated fluids were sterile and the eosinophile content ranged up to 100 per cent. Coincidentally with the asthmatic attacks and serious membrane reactions, there appeared electrocardiographic abnormalities in the deflections and amplitudes of the P waves and QRS complexes. These returned to normal with the termination of the asthmatic attacks in twelve of the cases and were irreversible in the four who died. Increase in blood eosinophilia in all cases, ranging at times to 84 per cent, as well as augmentation of the eosinophile granulocytes in the bone marrow were outstanding features. Recurrent skin lesions were characterized by urticaria, angioneurotic edema, purpura, and hemorrhagic necrosis in one case. Biopsies of the cutaneous lesions, including a subcutaneous nodule from Case 13, disclosed perivascular infiltrations with eosinophilia, collagen necrosis, as well as periarteritis nodosa observed in sections of the subcutaneous nodule.

The chief pathologic changes responsible for the clinical manifestations in the four cases that came to autopsy were found to be due to varying degrees of hyperergic and anergic vascular reactions in the lungs, the myocardium, serous membranes, etc. These reactions were characterized by thickening of the intima of small vessels, necrotizing arteritis, endoarteritis obliterans, and fibrosing arteritis.

1. The simultaneous precipitation of both the asthma and the polymorphous vascular reactions in these cases by the same allergenic stimulation lends support to the concepts (a) that bronchial asthma is fundamentally an expression of hyperergic vascular response which may be reversible or irreversible, and (b) that the accompanying resultant pathologic vessel changes do not represent disease entities but rather qualitative and quantitative degrees of perergic and anergic responses.

2. The syndromes dependent on such vascular reactions in the myocardium, pericardium, and other serous membranes, expressed as cardiac insufficiency, constrictive pericarditis, or polyserositis, may therefore be attributed to an allergic mechanism.

*Mucus Acid and Water Secretion in the Stomach Following the Injection of Pilocarpine.* F. HOLLANDER AND J. STEIN. *Am. J. Physiol.*, 140: 136, November, 1943.

Pilocarpine, when injected subcutaneously into stomach pouch dogs in adequate dosage, stimulated the flow of gastric HCl and fluid in amounts comparable with those evoked by histamine. Administration of pilocarpine was accompanied also by the secretion of gastric mucus in considerable quantity. The rate of secretion, however, did not differ materially from that of the "spontaneous" secretion of mucus in acid-free pouches. Furthermore, a

major part of this mucus-secretory activity was eliminated when the retention technique was used for collecting the pouch contents, thus demonstrating the mechanical origin of the mucus which is ordinarily evoked by this stimulus. Evidence indicates also that a considerable part of the mucus is squeezed out from the surface epithelial cells by the muscular activity induced by the pilocarpine, even in the absence of rubbing by a foreign body. Hence it is questionable whether any of the mucus-secretory activity is induced by direct action of the pilocarpine at the neuro-glandular junction. High dosages of the drug (0.5-1.0 mg./g.) induced restlessness, salivation, mucosal bleeding, vomiting and defecation. Oozing of blood in the pouch occurred to a greater extent in the continuous collection experiments than in those performed by the retention technique.

*Cutaneous Reactions Due to the Body Louse.* S. M. PECK, W. H. WRIGHT AND J. Q. GANT, JR. J. A. M. A., 123: 821, November, 1943.

Repeated exposures to the body louse will result in the development of a dermal hypersensitivity to it in the majority of those exposed. The feces of the louse play an important role in this induced reaction. There are apparently two components due to the "louse bite reaction"; viz.: (a) The purpuric element due to the act of feeding and (b) the development of an inflammatory reaction following sensitization. The pruritus accompanying infestation with lice seems to be mainly a part of the syndrome of hypersensitivity.

*Studies on Ionone. II. Optical Resolution of dl- $\alpha$ -Ionone.* H. SOBOTKA, E. BLOCH, H. CAHNMANN, E. FELDBAU, AND E. ROSEN. J. Am. Chem. Soc., 65: 2061, November, 1943.

The resolution of dl- $\alpha$ -ionone was accomplished by means of *l*-menthydrazone. The use of optically active  $\alpha$ -ionone as an indicator for the stability of the double bond system in ionone and its derivatives in certain important synthetic procedures is discussed.

*Cold Hemagglutination—An Interpretive Review.* D. STATS AND L. R. WASSERMAN. Medicine, 22: 363, December, 1943.

The entire literature on the subject of cold agglutination of erythrocytes and related subjects is reviewed. Clinical laboratory abnormalities which may indicate the presence of a cold hemagglutinin are pointed out. The occurrence of cold hemagglutination in acute infectious diseases, hematologic disorders, tropical diseases, cirrhosis of the liver, Raynaud's syndrome, pregnancy, venous thrombosis and gangrene is described. The differences between syphilitic paroxysmal cold hemoglobinuria and paroxysmal cold hemoglobinuria associated with cold hemagglutination are tabulated. The effect of external temperature on the sedimentation rate of blood with and without cold hemagglutinins is shown. Certain chemical and physical properties of cold hemagglutinins are described.

*Lymphosarcoma of the Intestines.* A. WINKELSTEIN AND M. H. LEVY. Gastroenterol, 1: 12, 1093, December, 1943.

Lymphosarcoma of the intestines is a rare disease in which the small intestine is more often affected than the large bowel. Multiple intestinal lesions are not uncommon. While the average age incidence is 43.7 years, it may occur at any age. The histologic differentiation into small cell lymphosarcoma and reticulum cell sarcoma is unimportant clinically. Abdominal pain, loss of weight, pallor, and abdominal mass or masses are the chief symptoms. There is frequently a characteristic, practically diagnostic sigmoidoscopic picture resembling the surface of the brain. Sooner or later, intestinal lymphosarcoma becomes a systemic disease which is invariably fatal. With surgical removal plus radio-therapy, the duration of life is usually less than one year. Occasional cases live several years.

*A Contribution to the Pathology and Therapy of Dysarthrias Due to Certain Cerebral Lesions.* E. FROESCHELS. J. Speech Disorder, 8: 301, December, 1943.

A survey of the etiology and pathology of dysarthrias caused by pyramidal and by extrapyramidal lesions is followed by the description of some phonetic methods for analytic

investigation of breathing, voice and articulation. As to the therapeutic procedure, the writer cautions against beginning with speech exercise before the muscles have been brought into the best possible balance. Pushing the fist down from the pectoral area during the emission of sounds and syllables helps to strengthen the speech muscles. On the other hand manipulating the jaw to the side during speech exercises is a means for relaxation for the muscles. The article is concluded with case histories and special exercises for every sound.

*Incarcerated Inguinal Hernia Containing a Cancer of the Bladder.* G. D. OPPENHEIMER. *J. Urol.*, 50: 6, December, 1943.

This report describes a unique experience concerning an 81 year old man who was operated on for an incarcerated inguinal hernia. A primary carcinoma of the bladder was found in the hernia, resected through the inguinal incision and the bladder closed. The patient recovered without complication or urinary leak and with primary wound healing. The pathologic report was "bladder wall infiltrated by transitional cell carcinoma."

*Hypertension in Only One of Identical Twins.* M. FRIEDMAN AND J. S. KASANIN. *Arch. Int. Med.*, 72: 767, December, 1943.

The presence of hypertension in only one of identical twins is reported. Results are given of a routine physical examination, a psychologic assay, an electrocardiographic study, and determination of the renal blood flow and of the glomerular filtration rate of each twin. Kidney function tests revealed that the renal blood flow was similarly reduced in both the normotensive and the hypertensive twin, and that the glomerular filtration rate in each was also similar. Electrocardiograms of the hypertensive twin revealed definite evidence of myocardial damage while the tracing made for his brother was essentially normal. Other than the cardiovascular differences noted, the contrasting personalities of these identical twins composed the only striking difference observed. The healthy twin was always more robust physically and intellectually more alert than the hypertensive twin. The hypertensive twin was by far the more dynamic of the two, more aggressive, more energetic, more conscientious, and more active socially than his well brother. It is suggested that the element of rivalry, with constant repressed hostility, was the motivating factor of his success; but on the other hand may also have been responsible for his hypertension. The evidence presented in this report suggests that renal ischemia is an incidental factor, not a causative one, in the pathogenesis of clinical hypertension. The similarity in the heredity and early environment of these identical twins stresses the divergency in personality drives as a possible cause of the hypertension found in one of them.

*Repair of Cranial Defects.* J. BERBERICH. *Practica oto-rhino-laryngologica*, 4:238, 1943.

The skull has a special importance as far as the healing of fractures is concerned. X-ray examinations of skulls many years after the fracture has occurred show that the fractures heal chiefly by connective tissue formation; in a few cases one finds isolated spots at the margin of the fracture where new bone formation has taken place. I never found a complete real bony closure of a fracture of the skull. These findings refer as well to fractures of the base and calvarium of the skull as to defects caused by trepanation and operation. In contrast to the findings in human beings are those in animals. In rabbits and guinea pigs trepanations of any kind heal with bone formation within a very short time.





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## THE EDWARD GAMALIEL JANEWAY LECTURES

## I. VITAMIN K, ITS DISCOVERY, BIOCHEMISTRY AND APPLICATION IN MEDICINE\*

HENRIK DAM, Sc.D.

*Associate member of the Rockefeller Institute for Medical Research*

In 1928-30 I carried out, in the biochemical institute of the University of Copenhagen, some studies on cholesterol metabolism in chicks. It was then already known that rats, mice and dogs can synthesize cholesterol but some experiments had been published which seemed to show that chicks could not thrive on a diet from which the sterols had been removed by extraction. When these experiments were published by Gardner and Lander in 1914, the role of fat soluble vitamins was not very well recognized, and I therefore found it desirable to repeat them using artificial, practically sterol-free diets to which vitamins A and D were added in the form of sterol free concentrates made from cod liver oil, or of small amounts of cod liver oil of known cholesterol content. Chicks were reared on such diets for different lengths of time from the day of hatching and the amount of cholesterol in their excretions and their body was determined and compared with the cholesterol content in newly hatched chicks from the same litter. It was thereby found that a considerable part of the cholesterol which the newly hatched chick has taken over from the egg yolk disappears during the first 2 or 3 weeks, whereafter cholesterol is formed in increasing amount as the body weight increases. Chicks therefore are able to synthesize cholesterol, just as well as are rats, mice and dogs, and they are also able to break it down.

Of still greater interest than this finding was, however, the unexpected symptom which appeared in some of the chicks which were kept on the diet for more than 2 or 3 weeks. They exhibited hemorrhages under the skin, in muscles or other organs, and blood occasionally taken out for examination showed delayed coagulation.

The lack or low content of cholesterol in the diet could not be the cause of the hemorrhages, since the experiments showed that chicks can synthesize cholesterol. Furthermore the hemorrhages also appeared in chicks which received a daily supplement of cholesterol.

The low amount of fat in the diet could, apparently, also be ruled out as a cause of the symptom since it was found that linseed oil and triolein could not prevent its appearance. It did not seem likely either that the tendency to hemorrhage was a manifestation of scurvy, even though the artificial diet had not been supplemented with vitamin C. Other authors had already reported

\* Lecture delivered in the Blumenthal Auditorium, The Mount Sinai Hospital, New York, October 30, 1945.

that chicks do not require vitamin C, and daily ingestion of lemon juice to a few of the chicks also proved to be ineffective.

In 1931 the hemorrhagic disease in chicks was described by a group of Canadian workers, McFarlane and others of the Ontario Agricultural College. They reared chicks on artificial diets in order to examine their requirements of vitamins A and D, and they observed hemorrhages and delayed clotting of the blood when identification bands were inserted in the wings. The hemorrhages appeared when the diet contained ether-extracted fish or meat meal as the source of protein, but not with ordinary fish or meat meal. They did not follow these observations further.

At this stage of the development I had to interrupt the work with chicks because of absence from my laboratory in Copenhagen until the fall of 1933.

In the meantime Holst and Halbrook at the University of California had also observed the disease and found that it could be prevented by fresh cabbage. They drew the rather sweeping conclusion that the protective factor in the cabbage was vitamin C, and that previous claims to the effect that chicks do not need this vitamin in their diet, were incorrect.

Shortly thereafter, pure vitamin C became available, and when taking up the work again, I could easily show that parenteral injections of Ascorbic acid failed to prevent the disease, thus excluding the possibility that the disease had anything to do with a destruction of vitamin C in or poor absorption of this vitamin from the intestine under the artificial dietary regime.

The salt mixture could be varied considerably without influence on the disease, and wheat germ oil was without protective effect, whereas a high content of cereals and seeds in the diet prevented the symptom. It was therefore safe to announce that the new experimental disease was due to the lack of a hitherto unrecognized factor in the diet. This was done in 1934.

Then a number of animal organs and plant material were examined for their ability to protect against the disease and it was found that green leaves and hog liver were among the most potent sources. It was also found that the factor was fat-soluble, and in 1935 it was characterized as a new fat soluble vitamin and given the designation vitamin K. The letter K was the first one in the alphabet which had not, with more or less justification, been used to designate other vitamins, and it also happened to be the first letter in the word "koagulation" according to the Scandinavian and German spelling.

The existence of vitamin K was promptly confirmed by Almquist and Stokstad at the University of California, Berkeley.

In the following few years aided by several coworkers I carried out an intense study on the way how the new vitamin acted on the blood clotting, how it could be concentrated and whether it played any role in other animals and in humans. Almquist and co-workers also continued their work at Berkeley, mainly on the concentration of the factor.

The hemorrhages in vitamin K deficiency develop in a way that minute vascular lesions caused by minor mechanical trauma are not closed by rapid clotting, as is the case in normal animals. This causes a continuous oozing of blood from the impaired region.



According to the accepted theory the process of blood coagulation may be separated into two stages.

1) The activation of a proenzyme, *Prothrombin* normally present in blood plasma, into an enzyme, *Thrombin*, by the action of *Thromboplastin* or *Thrombokinase* as it is also called. *Thromboplastin* occurs in tissue cells and in blood platelets (thrombocytes) and comes in contact with plasma when tissue is injured or when thrombocytes disintegrate through adherence to the surface of a wound.

Calcium ions are necessary for this part of the process: the thrombin formation.

2) The conversion of *Fibrinogen* into *Fibrin* by the action of thrombin.

It is easy to show that it is *prothrombin* and no other component which is lacking when vitamin K has been withdrawn from the diet. It can also be shown that prothrombin precipitated from blood plasma of normal chicks can bring the coagulation power back to normal when added to blood from vitamin K deficient chicks. (This was shown by Dam, Schoenheyder and Tage-Hansen, 1936.)

The use of chicks in the study of vitamin K deficiency has the advantage that these animals develop the disease very easily and it also simplifies the examination of the blood coagulation since in chicks and other birds thrombocytes do not play any important role in furnishing the blood with thromboplastin, as is the case in mammals.

Thus it is easy to collect a sample of blood from an artery and centrifuge and treat it in different ways without risk of spontaneous clotting. The only prerequisite is that admixture of tissue juice is carefully avoided.

In order to produce the disease in chicks it is necessary not only to give them a vitamin K free diet, but also to keep them under very clean conditions so that they do not soil their food and water with feces. Almquist and Stokstad were the first to report that vitamin K can be formed by putrefaction so that even when no vitamin K is present in the diet, the feces of chicks will contain it.

The reason why these animals so easily suffer from the disease when deprived of vitamin K may be due to the fact that in chicks the large intestine is short as compared to that of rats and rabbits. Vitamin K formed by intestinal bacteria is therefore not absorbed to any great extent in the chick.

An exact estimation of the clotting power of the blood reveals the fact that the vitamin K deficiency disease begins to develop a few days after vitamin K has been taken away from the diet, but the full development, i.e. reduction of the prothrombin to about 1 per cent of the normal value, requires a longer time, say 14 to 28 days.

The prothrombin level seldom falls to zero and therefore coagulability is not completely lost. It is sometimes found that hemorrhages in vitamin K deficient chicks stop spontaneously and are resorbed without alteration of the diet and without increase of the prothrombin content.

*Estimation* of vitamin K can best be carried out by determining the prothrombin content of blood before and after the ingestion of the substance to be tested and running a similar experiment with a standard vitamin K preparation.

I shall not bother you with a detailed account of the methods for Prothrombin determination but just mention a few principles which are or have been in use.

1) The method of Smith, Warner and Brinkhous. They first remove the fibrinogen from the plasma by addition of a very small amount of purified thrombin. The excess of added thrombin disappears by itself on standing for about 15 minutes. Then the prothrombin is converted into thrombin by the addition of thromboplastin, and finally the activity of the thrombin is measured against a pure fibrinogen solution. This method is called a 2-stage method because the two stages of the coagulation process: Thrombin formation and fibrin formation are separated. It is believed to be very accurate but is more cumbersome than the usual clinical method indicated by Quick.

2) Quick's method is a one-stage procedure: simply a large quantity of thromboplastin is added to the plasma or blood and the coagulation time is observed. Under these circumstances the coagulation time is largely determined by the amount of prothrombin and is therefore called the prothrombin time.

3) Taking advantage of the circumstance, that within certain limits low prothrombin can be compensated by using a higher concentration of thromboplastin, forms the basis of the method which was originally used in my laboratory in Copenhagen and was first tried by Schoenheyder.

When these different methods are used for human or mammalian blood it is necessary to prevent spontaneous clotting of the blood by thromboplastin set free from the platelets. This is done by adding oxalate or citrate to the blood thus removing the calcium, and again adding calcium when the conversion of prothrombin into thrombin shall start. It is also possible to make use of heparin.

The Unit for vitamin K activity was originally defined in our laboratory as that quantity which must be given daily per g. body weight of the chick in three days in order to bring the prothrombin value up from a very low level to the normal value. Now when a series of pure substances with high vitamin K activity are available, it is a natural thing to define the unit by means of one of these substances or to express the activity in terms of micrograms of one of the two natural K-vitamins which I shall mention later.

In *plants* vitamin K is found principally in all kinds of green leaves; leaves which have grown in the dark and therefore have not formed chlorophyll are poor sources. Tomatoes are a good source, but otherwise most fruits contain little vitamin K. Ripe cereals, beans and peas contain little. Carrots, potatoes and beets are practically free from vitamin K. Saprophytes such as mushrooms contain very little if any. Vitamin K is thus largely associated with chlorophyll, but it does not necessarily disappear from a plant organ when the chlorophyll disappears. It remains in tomatoes after they become red and in leaves after they become yellow in the fall. Yeast does not contain vitamin K but certain bacteria are very rich in this vitamin. *B. Coli* is much richer than *acidophilus*. Its function in these organisms is unknown, but in the green plant it may have something to do with the photosynthetic process. It occurs in the same morphological parts of the plant cell as chlorophyll, xanthophyll and carotene, namely in the chloroplasts. Vitamin K from green plants is called  $K_1$ .

Chemically it differs slightly from vitamin K formed by putrefaction which is called K<sub>2</sub>. This difference was first noticed by Doisy and coworkers.

In the *animal* organism vitamin K does not occur as abundantly as in plants. In chickens small quantities only are deposited in the different organs or in the eggs. The mammalian organ which hitherto has been found to contain most vitamin K is the liver of pigs. Cow's milk and human milk are rather poor sources. Feces are rich in vitamin K formed by the putrefaction bacteria in the large intestine.

Before I proceed to a more detailed discussion of the mode of action of vitamin K, it will be convenient to consider briefly the most essential features of its chemistry.

Vitamin K<sub>1</sub> can be extracted by fat solvents from dried leaves, dried alfalfa for instance. It can be concentrated by the removal of chlorophyll by selective adsorption, by chilling of an acetone solution of the remaining material, whereby crystalline non-active substances are removed, by molecular distillation at a pressure of one thousandth of a millimeter mercury and 115–140 degrees centigrade, whereby the vitamin passes up on the condenser, and final purification by repeated chromatographic adsorption. The preparation of pure vitamin K from green leaves was first reported by Dam, Karrer and coworkers, 1939. The pure vitamin is a yellow oil. It consists of carbon, hydrogen and oxygen, gives a characteristic color reaction with sodium ethylate and shows an absorption spectrum in the ultraviolet.

The elucidation of its constitution was accomplished by Doisy and coworkers, and by Fieser and coworkers.

Doisy and coworkers also prepared pure vitamin K<sub>2</sub> from putrefied fishmeal and showed that this substance was crystalline at room temperature. It melts at 54 degrees centigrade and gives a color reaction and an ultraviolet spectrum similar to that of K<sub>1</sub>.

Both substances are derivatives of 1,4-naphthoquinone. They are easily destroyed by saponification and by light.

Vitamin K<sub>1</sub> is 2-methyl-3 phytyl- 1,4-naphthoquinone (phytyl is the radical of the high molecular alcohol phytol which also forms a part of the chlorophyll molecule). Vitamin K<sub>2</sub> has a similar structure but the long side chain is different from phytyl; it is longer and has more double bonds.

The methyl is essential for activity, but not the phytyl group. In accordance herewith 2-methyl-1,4-naphthoquinone has a high activity, as first reported by Ansbacher and Fernholz, 1939. This substance is now official in the U.S.P. under the name of Menadione. The hydroquinones of the natural K-vitamins as well as of menadione are also active and so are their esters. Some of these (artificially prepared) esters are water soluble and useful for parenteral injection. This applies to the diphosphate "Synkayvite" described by Lee and Foster, for instance.

Almquist and Klose reported, 1939, that the orange pigment Phthiocol, of the tubercle bacillus has a slight vitamin K activity. Phthiocol is 2-methyl-3 hydroxy-1,4-naphthoquinone.

We will now return to the *mode of action* of vitamin K in the animal organism.

When the vitamin is given intravenously, it is possible to study the effect at different intervals from the moment of introduction into the blood stream. It is thereby revealed that the action does not set in instantaneously but requires a certain time for its development. If the prothrombin content is about 1 per cent of the normal value at the starting point, it takes about 5 hours to raise it to 50–100%, assuming that a sufficient amount of vitamin K is injected.

The prothrombin level is normal on the day after injection, thereafter it again returns to low values.

When vitamin K is added *in vitro* to the blood from a K-free animal, no improvement of the prothrombin content is observed, even when the vitamin has remained in contact with the blood for many hours at body temperature before the clotting power is tested. This observation suggests that the action of the vitamin takes place within the *tissue* cells.

Andrus, Lord and Moore, 1939, excised the liver in normal dogs and studied the prothrombin level with and without ingestion of vitamin K and bile salts. They found that the blood prothrombin decreased in both instances, indicating that the liver is necessary for the action of vitamin K.

Several other observations also show that the liver is the organ concerned with prothrombin formation. Thus Warner found (1938) that removal of  $\frac{2}{3}$  of the liver in rats resulted in a decrease of prothrombin. Intoxications involving severe damage to liver tissue also lead to a fall in prothrombin. This is found, for instance, after the intake of chloroform (Smith, Warner and Brinkhouse, 1937). Vitamin K does neither prevent nor cure hypoprothrombinemia of this origin.

Further it is known that vitamin K does not alleviate the prothrombin deficiency in patients whose liver parenchyma is severely damaged.

At this point I shall mention briefly the substance dicoumarol which is formed in so-called "spoiled" sweet clover hay, and is now prepared synthetically. Dicoumarol causes low prothrombin probably by reducing enormously the prothrombinogenic action of vitamin K in the liver.

As to the manner in which vitamin K affects the formation of prothrombin two alternatives may be considered. The first is whether vitamin K is a constituent of prothrombin. Prothrombin is a protein. It accompanies the globuline in many precipitation reactions and does not dialyse. Therefore, and because of the time factor in the development of the action, vitamin K cannot be identical with prothrombin. But one could imagine that vitamin K might enter the prothrombin molecule as a prosthetic group, just as hem does in hemoglobin. However, this is not very likely. If vitamin K were present in the prothrombin molecule, one would expect prothrombin itself to act as vitamin K, so that the peroral ingestion of prothrombin would cure the prothrombin deficiency of K-free animals. Experiments in which we precipitated prothrombin from large amounts of normal hen's plasma (at pH 5.3) and gave it to small chicks living on a vitamin K-free diet, did not show any definite vitamin K activity. The most likely explanation therefore is that vitamin K merely enables the liver cells to produce prothrombin.

The mechanism of this action is unknown. It is possible that the redox properties of the quinone groups play a role in an enzyme system which has to do with the formation of prothrombin.

As to vitamin K deficiency in *different species* of animals the following may be said: While the disease is most easily and regularly developed in chicks, young geese and ducks, by giving them a vitamin K-free diet, some rats may become just as ill as chicks, while in a group of rats many individuals may be resistant for a very long period of time. This is probably due to individual differences in the supply of vitamin K from bacteria in the large intestine. It has been reported that addition of sulfa drugs to the diet will cause a faster and more regular development of the symptom in rats (Kornberg *et al.*, 1944). Incorporation of a large amount of mineral oil in the diet of rats will minimize the absorption of vitamin K and thus facilitate the development of the deficiency disease.

*Rabbits* have been observed to develop the disease only to a moderate degree. These animals as well as rats eat feces directly from the anus during the night and thereby partially protect themselves against vitamin K deficiency.

The *absorption of vitamin K from the intestine* is a point of considerable interest. Several investigators have observed hemorrhages in dogs and rats in which the flow of bile into the intestine had been cut off by ligation of the bile duct or by a complete bile fistula through which the bile is made to flow steadily out of the body (Hawkins and Whipple, 1935; Vadsten, 1936; Greaves and Smith, 1937). Hawkins and Brinkhous (1936) showed that the bleeding tendency of bile fistula dogs is due to a low prothrombin level. Greaves and Smith (1937) showed that the deficiency in blood coagulation resulting from bile fistula in rats could be eliminated by giving these rats a diet very rich in vitamin K. Such experiments suggest the importance of bile for the proper absorption of vitamin K. In my laboratory in Copenhagen we have ligated the ductus choledochus in chicks and cured the resulting coagulation deficiency by intravenous injection of vitamin K. It could be shown that the effect of a given dose of vitamin K is quantitatively the same whether the vitamin K deficiency had been developed by means of a K-free diet or by ligation of the choledochus.

The first time that a *hemorrhagic disease in man* was recognized as a K-avitaminosis was in connection with the cholemic bleeding tendency. This bleeding tendency formerly constituted a great danger in operations on patients suffering from obstructive jaundice, say from gall stones or a tumor. This was found independently by Warner, Brinkhous and Smith, by Butt, Snell and Osterberg and by Dam and Glavind in the early part of 1938. Since then, the practical utilization of vitamin K in surgery has been tried by a large number of surgeons and its value has been fully established. It is possible, by suitable vitamin K treatment to eliminate completely the risk of bleeding in such patients, provided, of course, that the case is not complicated by severe damage of the liver so that vitamin K cannot act.

The bile acids are the constituents of bile which aid in the absorption of all fat-soluble substances. If the treatment of such patients is carried out with natural fat-soluble vitamin K given by mouth, it is necessary to give bile acids,



say desoxycholic acid, simultaneously with the vitamin in order to secure the absorption of vitamin K. It is easier to use one of the more or less water-soluble vitamin K active substances, which can be absorbed without bile or may be given by parenteral injection (10 mg. vitamin K the day before operation, repetition several times during the first two weeks after the operation).

Overdosage with vitamin K does not afford the danger of a too high coagulability of the blood since vitamin K cannot raise the prothrombin content much above the normal value. The fact that vitamin K cannot act when the liver parenchyma is sufficiently damaged, forms the basis of a liver function test.

A bleeding tendency due to reduced absorption of vitamin K from the intestine can also be observed in certain intestinal diseases, where profuse diarrhoea occurs and the intestinal mucosa is damaged. This has been found in cases of Sprue, for instance, where the absorption of fat is greatly diminished (Hans Hult, 1939, Mayo Clinic, 1939), or in ulcerative colitis.

The purely *alimentary* K-avitaminosis in man, that is, a lack of vitamin K due to an insufficient amount of the vitamin in the diet, is a rare disease on account of some vitamin K being supplied by intestinal bacteria. Experiments with a completely K-free diet have not been made with humans, but a moderate prothrombin deficiency which could be treated with vitamin K has been reported in some patients living on a very restricted diet (coffee and doughnuts, for instance) (Kark and Losner, Harvard University and Boston City Hospital, 1939).

A rather interesting occurrence of vitamin K deficiency is that of the *newborn* infant.

Low coagulation power of the blood of newborn babies was occasionally reported many years ago. Whipple described such cases in 1912 and found low prothrombin in a case of melaena neonatorum. The fact that a low prothrombin level which may be raised by treatment with vitamin K regularly occurs in newborn infants in the first week after birth was first recognized by Waddell and coworkers at Virginia University Hospital and independently found by several other workers—also at the University of Copenhagen. This finding has been further studied by a large number of investigators.

There is a marked prolongation of the coagulation time right at birth, but the prolonged clotting times are seen most frequently on the 3rd day. Thereafter they decline toward normal values.

In a group of 43 infants without any actual bleeding, aged from 0 to 7 days, 18 were found to have prothrombin values lower than 20 per cent of the normal value for adults. Twenty per cent prothrombin is approximately the limit of the danger zone. This means that these 18 babies were in danger of incessant bleeding if they were exposed to rough handling or surgical operation.

In a group of babies with actual bleeding the prothrombin may be very low.

The frequency of cases with bleeding is said to be about 1 per cent of all newborn babies, but this represents only the number of cases with easily detectable bleeding. A closer examination for hemorrhages reveals a much higher figure.

The bleeding may come from the umbilicus, the intestinal tract, the skin or the cerebral vessels.

Treatment with vitamin K raises the prothrombin to approximately normal values in 24 hours. The most rational treatment is to give parturient mothers vitamin K some hours before delivery.

This treatment does not result in completely normal prothrombin levels in the babies in all cases, but the values lie between 20 and 100 per cent of the normal value for adults, that is, above the danger zone.

How important the treatment with vitamin K is in preventing death among the newborn during or shortly after birth appears clearly from several statistics presented in this country, for instance, by Beek in Brooklyn and Hellman at Johns Hopkins Hospital, according to which the treatment of mothers has cut the total death rate among the newborn from 4.6 per cent without treatment down to 1.8 per cent in the treated groups.

We will now consider the *cause* of the lack of vitamin K in the infant.

The investigations of Tage-Hansen and of Thordarson in Denmark have shown that the mother's prothrombin content is increased at the end of pregnancy; the increase may amount to 50 to 100 per cent of the value before pregnancy. This does not suggest that the mothers lack vitamin K. Nevertheless, the newborn child is K-deficient. The simplest explanation of this is that the placenta does not let natural fat soluble vitamin K pass freely into the circulation of the fetus.

That the prothrombin level decreases further during the first days after birth is not surprising because the supply of vitamin K is low. This is due to the initial sterility of the large intestine and to the low intake of milk in the first few days.

The reason why the prothrombin level normally rises again in the course of some days is to be sought in the increasing bacterial flora together with the increasing volume of the contents of the large intestine, whereby the bacteria have more substrate to act upon.

Milk itself contains only little vitamin K but the daily vitamin K requirement of the baby is very low (about 1 to 10 gamma per day), so that it may be that the low vitamin K content of the milk nevertheless has some importance.

There are a few other fields where vitamin K therapy may become necessary:

Thus in treatment with sulfa drugs the intestinal flora may become so reduced that the supply of vitamin K from this source is largely cut off. If the diet does not contain enough vitamin K bleeding tendency may arise.

Excessive and uncontrolled intake of mineral oil may interfere with the absorption of vitamin K.

It has been claimed by some authors that hemoptysis in patients with pulmonary tuberculosis is associated with low prothrombin and should be treated with vitamin K. I believe that this is wrong. An investigation of this question was undertaken in Copenhagen by some of my associates, and it was not possible to find either hypoprothrombinemia or any beneficial effect of vitamin K treatment of such cases. It is also difficult to understand why there should be vitamin K deficiency in this disease.

Salicylate treatment has also been said to incur hypoprothrombinemia which can be compensated by vitamin K. This seems worthwhile to investigate

further. A. Palladin (1945) has claimed that vitamin K acts in almost any kind of hemorrhagic condition but this does not seem to be established by controlled experiments.

Menadione, the official substitute for vitamin K has been reported to interfere with the bacterial formation of lactic acid from carbohydrates, and it has been suggested that it might counteract dental caries when incorporated in chewing gum. Other quinones inhibit lactic acid formation by bacteria, without having vitamin K activity. It therefore seems highly unlikely that vitamin K as such should play any role in the prevention of caries.

As matters stand at present, vitamin K therapy is only relevant against diseases which incur bleeding tendency due to low prothrombin and not against such hemorrhagic diseases as hereditary hemophilia, thrombocytopenia or scurvy.

#### BIBLIOGRAPHY

The literature cited in this lecture is listed in two articles by the author: Vitamin K, its chemistry and physiology. *Advances in Enzymology*, 2: 285, 1942; Medical aspects of vitamin K. *The Journal Lancet*, 63: 353, 1943; and in an article by PALLADIN, A.: *American Review of Soviet Medicine*, 2: 267, 1945.

## THE VISCERAL MANIFESTATIONS OF KAPOSI'S SARCOMA<sup>1</sup>

DANIEL STATS, M.D.<sup>2</sup>

Medical literature contains numerous references to the rare disease first described by Moritz Kaposi (1) as idiopathic multiple pigment (hemorrhagic) sarcoma of the skin and known since as Kaposi's sarcoma. In most instances the communications have been made by dermatologists and the cutaneous manifestations of the disease have received major attention. These changes are usually so typical that an experienced dermatologist can diagnose the disease by inspection.

It has been known for many years that the viscera and lymph nodes may become involved by a similar sarcomatous process (2, 3, 4, 5, 6). Because of this the disease is of general significance and must be considered in the differential diagnosis of a large group of systemic complaints and physical findings. In the first cases of this type observed, the visceral involvement followed the appearance of the cutaneous disease. More recently (Case 1) and (3, 4, 7, 8, 9), it has been noted that the involvement of internal organs may precede the appearance of Kaposi's sarcoma of the skin; some (7) maintain that the cutaneous lesions may be lacking altogether. It must be pointed out, nevertheless, that many cases of Kaposi's sarcoma of the skin progress slowly for many years and have been examined at autopsy without any indication of spread beyond the dermal apparatus.

In the present state of our knowledge, it is fruitless to speculate concerning the nature or etiology of Kaposi's sarcoma (2, 10); there is good agreement that this disease should be classified with the tumors. The individual lesions behave as neoplasms, usually for a time benign, but after a longer or shorter interval assuming malignant characteristics. There is no unanimity concerning the origin of the tumor. Fibroblasts, perithelial and endothelial cells, myoneural structures of the glomus, reticuloendothelial elements and others have been considered by various authors as the starting point of the new growth. The minority view the disease as a local skin disease, which, when involving the viscera, should be considered as a malignant tumor with metastases. Most investigators point out that the bizarre localizations of the internal lesions, their appearance prior to the skin manifestations and the lack of invasive tendencies in the tumors favor a multicentric origin. Some of these look upon the disease as a systemic disturbance of angiomatous or reticuloendothelial nature (11, 12, 13).

Histologically (2, 6), the developed lesion has the appearance of a sarcoma of a varying degree of malignancy in which connective tissue and endothelial elements predominate but in which one also finds a conspicuous number of thin-walled and malformed ectatic vascular spaces. Secondary features include

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hemorrhage, necrosis, lymphocytic infiltration and pigmentation. The lesions commonly are circumscribed but not encapsulated.

Before considering in detail certain special manifestations of this disease, it would be well to list catagorically the sites of predilection. The most frequent sites after the general skin include the glans and preputium penis, the submucosa of the gastro-intestinal tract, the upper and lower respiratory tracts and the superficial and deep lymph nodes. Unusual localizations may be noted in the serous membranes, spleen, liver, suprarenal glands, myocardium, mesentery, diaphragm and urinary bladder. In other sites, the lesions are excessively rare or do not occur.

Clinically, the tumors make their presence known either by their size, hemorrhage or irritation of a serous membrane leading to an effusion into a serous sac (pleura or pericardium) (Cases 2, 3, 4). The fluid is often of a hemorrhagic nature and may be xanthochromic. It has a tendency to recur; ascites of significant degree has not been described.

As will be observed from examination of the appended case reports, swelling of the extremities is common in Kaposi's sarcoma. This may be the first manifestation of the disease and may precede any other lesion by months or years (Case 1) and (5, 17, 18). In other instances swelling may occur late in the course. The edema is of several varieties.

It may take the form of pitting edema. This is in many ways superficially similar to the edema seen in other diseases, e.g., congestive heart failure. It is usually symmetrical and alleviated to a certain degree by elevation of the part. It sometimes has the unusual tendency (Cases 1 and 3) of terminating sharply below the knee, the foot and leg being several times larger than normal in size while the knee and thigh are of normal proportions. At other times the thigh shares in the process. A similar picture has been observed in the upper extremities. The cause of this edema has never been satisfactorily explained. It may occur in patients with normal blood serum albumin levels; lymph drainage so far as can be ascertained seems to be normal, since the regional lymph nodes may be little or not at all involved by disease; mechanical static factors do not appear to be of importance in this regard; there are no known irritative influences acting on the capillaries. It is important to keep this rare disease in mind in cases of unexplained edema. At times other evidence of Kaposi's sarcoma is present; occasionally, accurate diagnosis must be held in abeyance until such manifestations appear.

On other occasions the skin lesions acquire a locally infiltrative character assuming the aspect of plaques and producing a rough boardlike swelling of one or several extremities. Marked enlargement may result from such a process; the tissue augmentation can be ascribed to tumor infiltration in the skin (4, 7, 15). Blockade of lymph drainage either by local infiltration in lymphatics or regional obstruction at the trunk by disease in the lymph glands may be added (5, 6, 7).

Thickening of the collagenous tissue in the neighborhood of skin nodules may further impede lymph drainage and accelerate the swelling (14). Several



authors (12, 16) have commented on localized sclerodermatic skin changes in the extremities or trunk as a cause of swelling and a similar process was noted in Case 3.

Sometimes the amount of swelling is affected to some degree by local hemorrhage. A hemorrhagic tendency in this disease has been described from time to time (4, 5, 19, 20). This takes the form of large subcutaneous hematomas, purpura, or bleeding from a mucosal tumor. Infrequently a generalized purpuric state may be observed. Certain of these manifestations are readily explained by the histology of the Kaposi lesion. Hemorrhage is the usual microscopical finding; its origin can be found in the telangiectases. Some of the cutaneous bleeding can be ascribed to this since it occurs in close proximity to nodules or plaques. In other instances, however, purpura occurs in what appears to be normal skin. During the process of resorption of such hematomas, clusters of Kaposi nodules may appear in the area of fading purpura (2). In the few cases in which studies have been made, no abnormalities of the bleeding or clotting mechanism have been found to account for such bizarre manifestations. Excessive bleeding does not occur from operative wounds. Mucous membrane bleeding is always, so far as is known, due to hemorrhage from a Kaposi nodule. Excessive epistaxis or bleeding from the gums has not been noted.

From the clinical point of view superficial lymph node enlargement is usually observed when skin lesions are present. The latter, however, may be small and relatively inconspicuous. The inguinal nodes are involved most often. This should not lead to the assumption of metastases from the oft-present skin lesions in the lower extremities, for lymphadenopathy frequently occurs without anatomic relation to skin lesions (Cases 2 and 3) and (5, 20). Considerable generalized superficial lymphadenopathy may occur even when the skin lesions are few and localized to the legs. The nodes may vary greatly. They may be 1 to 2 cm. in longest diameter, movable, painless, rubbery, smooth and distinct (Cases 2 and 4). In other instances they may become adherent and fused together to form a mass 6 or more cm. in greatest dimension (Case 3). They are usually described as firm and apparently are rarely stony hard. Evidence of an inflammatory reaction with liquefaction and ulceration has not been described. As mentioned previously, involvement of the lymph channels and nodes may be responsible for some of the swelling of extremities. On the other hand, marked lymph node enlargement may occur without obvious lymph stasis. It has been stated that lymph node enlargement, usually but not necessarily, occurs when sarcomas ulcerate or become secondarily infected (2). In many instances, however, this was not observed to be the case. It is clear that the superficial lymph node enlargement in this disease has many aspects in common with the large group of local or generalized lymphadenoses. The presence of the typical skin lesion should allow, in many cases, the diagnosis of Kaposi's sarcoma. However a common diagnostic error when both are present is to diagnose leukemia with infiltration of the skin. Blood or bone marrow study will decide this question.

Though enlargement of the deep lymph nodes is often more extensive than the superficial ones, their situation renders clinical detection difficult. The most common nodes to be involved are the mesenteric and retroperitoneal groups, though all or any may participate. Here again the node involvement is not necessarily regional to an organ involved with Kaposi nodules; therefore this involvement should not be viewed only as the result of a metastatic process. Enlargement of deep nodes can occasionally be ascertained clinically by the palpation of irregular masses in the abdomen or by roentgenologic or clinical evidence of mediastinal or bronchial lymph node enlargement.

The histological appearance of the involved lymph nodes may be identical with the skin tumors. The entire structure of the lymph node may be replaced. In certain instances, however, biopsy of enlarged lymph nodes failed to reveal tumor tissue (Case 1) and (4, 5 and 16). It is not possible at present to assess the significance of these findings; they may represent the early stages of lymph node alteration before actual tumor is present or may be evidence of secondary inflammatory change. Dörffel (2) stated that early involvement of lymph nodes was characterized by swelling and proliferation of endothelial cells in the blood vessels and in the supporting reticuloendothelial tissues of the nodes. Greppi and Bettoni (21) described round cell hyperplasia and Goldschlag (12) mentioned non-specific chronic inflammatory changes. MacKee and Cipollaro (4) stated that the nodes may show only an increase in plasma cells, phagocytosed iron pigment and some thickening of the stroma. In Case 4 we observed that in early lymph node involvement tumor appeared first in perivascular situations within the nodes. Often such nodes were entirely surrounded by Kaposi tumor which did not invade the capsule. However, Della Favera (5) described invasion by tumor of the capsules of such lymph nodes. He was the first to point out the fact that enlarged nodes may not show typical focal changes. In some such nodes he described the changes as limited to a thickening of the stroma.

Not infrequently lymph node involvement is so marked as to be considerably out of proportion to other visceral involvement by tumor. This may be construed as evidence favoring the general systemic nature of Kaposi's sarcoma and in this regard relates the disease with lymphoblastomas or reticuloendothelioses.

Pathological alterations in the spleen or clinical aberrations in its function have not been described frequently in the generalized form of Kaposi's sarcoma. Part of this may be due to incomplete observation since in our 4 cases, unquestionable changes were present in 3 and the fourth (Case 3) may have been involved as well.

Extreme enlargement of the spleen may be found in this disease. The largest organ weighed 1340 gm. (9) and in not a few instances weights over 700 gm. were recorded. The organ may extend anywhere from the costal margin down to the hypogastrium to the right of the midline occupying the entire left upper abdominal quadrant and considerable segments of the left lower quadrant and epigastrium. In Cases 1 and 2 the spleen was nodular and fixed to the posterior parietes.

The effect of a subcutaneous injection of epinephrine upon the size of the spleen was reported only once. Greppi and Bettoni (21) stated that the spleen in their case shrunk moderately. In our Case 1 no significant change in the size of the spleen was observed. In each of these instances histological examination of material obtained by splenic aspiration was reported. The Italian authors found 7 per cent neutrophilic polymorphonuclear leucocytes, 59 percent mature lymphocytes, 6 per cent histiocytes and 28 per cent monocytes, many of which were immature. In our case we found a wholly different formula with more lymphocytes and few histiocytes and monocytes.

There is great variation in the pathological appearance of the spleen in different cases. The spleen in Symmers' case 8 (14) weighed 1000 grams. The pulp was almost completely replaced by circumscribed tumor nodules. Paolini (22) described a case in which the spleen measured 20 cm. in its longest diameter. The normal architecture was replaced by many young tumor nodules disseminated throughout the organ. In addition there was myeloid metaplasia and the demarcation between the pulp and the Malpighian corpuscles was not distinct.

On the other hand in some cases of Kaposi's sarcoma with splenomegaly distinct tumor tissue could not be found in the spleen or, if present, it was not responsible for the enlargement. Greppi and Bettoni (21) found "arterial" hyperemia typical of the alterations in hemolytic states. Dalla Favera (Case 3) (5) stated that the spleen was moderately enlarged but did not contain tumor. In the case reported by Usseglio and his co-workers (9) the spleen contained many well circumscribed nodules. These consisted of large phagocytes filled with red cells. Tumor tissue was not found. In one case (17) the spleen was described as follicular.

Opportunity to examine the spleen was afforded in two of our cases. In Case 4 the organ was enlarged several times but was free of tumor. The Malpighian follicles were sharply delimited. In the pulp the reticulum cell hyperplasia was striking. Many of these cells were vacuolated or showed degenerative changes. In Case 2 the spleen weighed 700 grams; grossly, tumor nodules were not recognized. Some hemorrhage was present. Microscopically however, spindle tumor cells were observed in poorly circumscribed islands infiltrating the surrounding tissue (see case 1).

In the cases which we observed, striking alterations in the peripheral blood picture were not observed. The changes found were due in part to radiotherapy directed toward the skin or splenic lesions. Numerous authors have commented on the occurrence of alterations in the hemogram. These are rarely marked and never of specific nature. Monocytosis of considerable degree has been the most consistent finding. Also of passing mention is the mild anemia and occasional eosinophilia or lymphocytosis. The total white blood count is usually normal. The previously mentioned case of Greppi and Bettoni (21) is unique in that their patient had a microspherocytic hemolytic anemia with an enormous excretion of fecal urobilinogen. In addition the patient exhibited a marked granulocytopenia and died with oral sepsis. The case reported by

Usseglio (9) may have been similar. A moderately severe anemia and leucopenia were temporarily ameliorated by splenectomy. There was no definite evidence of a hemolytic process in that case.

In Cases 1 and 2 which we studied, examination of bone marrow obtained by sternal aspiration revealed an active or hyperplastic marrow with a normal differential count. Bertaccini (23) examined the bone marrow of three patients with Kaposi's sarcoma all of whom had a considerable monocytosis in the peripheral blood. In two of these patients he reported an increase in reticuloendothelial and monocytic cells in the marrow. He also stated that impression smears taken from Kaposi tumor nodules revealed monocytoid cells similar to those seen in the blood in certain cases of subacute bacterial endocarditis.

The significance of these various splenic, hemic and bone marrow deviations cannot be assessed. One is immediately struck by the great variability in findings. The material of some of the authors supports the idea that the reticuloendothelial system is gravely involved in this disease. The changes may be interpreted either as a reaction of this tissue to the presence of the tumor or a direct implication of this tissue in the process of neoplasia. Dörffel (2) has concisely presented some of the evidence in support of this thesis. Other authors have pointed to the simultaneous presence of Kaposi's sarcoma with mycosis fungoides (11), Hodgkin's Disease (12) and lymphatic leukemia (13).

Several articles have appeared in recent years stressing the thesis that Kaposi's sarcoma may exist as a primary tumor of the heart without cutaneous manifestations. This was pointed out simultaneously by Choisser and Ramsey (3) and Weller (9). They each described two cases (which appear to be the same patients) in which a hemorrhagic reticuloangiosarcoma of the right atrium was present and in one of which metastases occurred. Similar cases were described by Cunha Motta (25) and Aegerter and Peale (7). In none of these was the distribution of lesions similar to that seen in classical Kaposi's sarcoma with visceral involvement. The identity of such cases with Kaposi's sarcoma was based on the histological resemblance of the cardiac tumors with the common cutaneous tumors. So-called pseudomyxoma of the heart may have a similar structure (26). The fundamental question of the specificity of the microscopic anatomy of Kaposi's sarcoma will not be discussed further in this publication.

On the other hand, the cardiac involvement in Kaposi's sarcomatosis with skin involvement differs greatly from the cases mentioned above. The neoplastic involvement of the heart in true Kaposi sarcomatosis is incidental and does not give rise to symptoms. Symmers (14) described nodules of tumor in the epicardium. Dillard and Weidman (16) described one small nodule in the subepicardium of the left ventricle. In the cases observed by us several nodules were observed in the epicardium and myocardium of both ventricles in Case 2, while in another case (Case 4) with very extensive lesions, the heart was spared; several tumor plaques were observed in the parietal pericardium at the base.

Involvement of the gastrointestinal tract is characterized by circumscribed submucosal nodules less than 1.5 cm. in diameter which can be observed, because

of their purple color, through the serosa. On the mucosal aspect they are usually covered by intact epithelium and may be pedunculated. Ulcerations have been described (5 and 22) and occult blood was observed in the stools (14). In most instances lesions occurred in the stomach or small intestines; less often appendiceal or large intestinal involvement was mentioned (5, 16, 31). Lesions of the oral cavity, particularly the hard and soft palates (5, 22, 31) were frequently described. Literally hundreds of such nodules may be scattered throughout all segments from the mouth to the arms. As a rule there were no symptoms relative to the gastrointestinal tract. Intestinal perforation and intra-abdominal adhesions have not been described. Severe diarrhea and abdominal pain (22) and gastro-intestinal hemorrhage (7) may occur.

Practically all portions of the respiratory tract, excepting the nasal cavity, have been involved by tumor nodules. Nodules in the tongue (30) (Case 2), in the hypopharynx (8), larynx (29), trachea (5, 30), bronchi (5), pulmonary parenchyma and pleura (5) (Case 4) have been described. Tumor involvement as extensive as observed in Case 4 has not been mentioned in the literature. Despite such widespread lesions, symptoms related to such tumors are not common. In almost all instances the nodules remained small, well circumscribed and did not ulcerate.

#### ILLUSTRATIVE CASES

*Case 1. History* (Adm. #519917). The patient, a Russian tailor, aged 69 years, has been under observation for two years. Despite repeated careful study on four admissions to the Hospital, the cause of his splenomegaly and edema could not be ascertained until the typical skin lesions of Kaposi's sarcoma appeared.

His illness started two-and-one half years previously when he observed the appearance of a painless mass in the left upper abdominal quadrant. The mass proved to be an enlarged, grossly-nodular, freely-movable spleen, which could be palpated to the level of the umbilicus. Several small, hard, nodular lymph nodes were present in the posterior triangles of the neck and in the groins. The skin was free of any abnormalities. There was a pea-sized, circumscribed, purple nodule in the buccal mucosa.

*Laboratory data.* Laboratory examination on this and subsequent occasions revealed the following data. The hemoglobin was 78 per cent (15.5 G. = 100 per cent); the red cell count was 4,370,000 per cu. mm.; the white cells numbered 4700 per cu. mm. and the platelets 210,000 per cu. mm. The differential blood count revealed 58 per cent segmented neutrophils, 5 per cent non-segmented neutrophils, 4 per cent segmented eosinophils, 26 per cent lymphocytes, 7 per cent monocytes and 0.5 per cent reticulocytes. After radiotherapy (vide infra) the hemoglobin was 69 per cent, the white blood count 2000 per cu. mm. and the platelets 100,000 per cu. mm. Three sternal bone marrow aspirations were performed. The total nucleated count varied from 250,000 to 950,000 per cu. mm. and the megakaryocytes ranged between 514 and 110 per cu. mm. The differential counts did not vary considerably and were within the range of normal. Urine and stool examinations yielded normal findings. Blood chemical determinations showed the following: the sugar was 130 mg. per cent; the urea N was 18 mg. per cent; the icterus index was 5; the whole blood uric acid was 6.8 mg. per cent; the alkaline phosphatase was 10 King Armstrong units per 100 cc.; the total serum protein varied between 5 and 7.5 Gm. per 100 cc. and the albumin was always above 3 Gm. per 100 cc.; the cephalin-cholesterol flocculation was 3+; the total cholesterol was 160 mg. per cent while the ester fraction was 90 mg. per cent. The blood Wassermann and Kahn tests were negative; however, on later examinations the former was 2+ and the latter 3+. At this time the Kline diagnostic test was 2+; the Kline exclusion test was 3,4;



the Mazzini test was 3 + and the Kolmer test was 1 +. Subsequently the Wassermann and Kahn tests were both negative. Other examinations included a galactose tolerance test which was negative, a basal metabolic rate of +40 per cent; a bleeding time of 3 min., a coagulation time of 7 min., a prothrombin index of 100 per cent; a negative result in the tourniquet test, a normal erythrocyte sedimentation test, and a determination of the venous pressure in the femoral veins which was recorded as 3.5 cm. of blood. The spleen was observed not to change in size after the subcutaneous injection of 0.5 cc. of 1/1000 epinephrine hydrochloride. Differential count of material obtained by aspiration of the spleen revealed 78 per cent lymphocytes, 3 per cent non-segmented neutrophils, 11 per cent segmented neutrophils, 3 per cent segmented eosinophils, 0.5 per cent segmented basophils, 1.5 per cent monocytes, 0.5 per cent plasma cells, 1.0 per cent reticulum cells and 1 per cent normoblasts.

*Course.* Eight months after the onset, symmetrical pitting edema of both lower extremities, terminating sharply just below the knees, appeared. There were no skin nodules at this time. The edema disappeared almost completely after a night in bed. Shortly after this a universal, scaly, erythematous dermatosis appeared. Biopsy of the skin at this time revealed edema, venous congestion, hemorrhage into the subcutaneous fat tissue and chronic inflammation. Biopsy of a lymph node was reported as chronic lymphadenitis. The dermatosis cleared spontaneously in ten days.

About fourteen months after the onset, pea to bean-sized flat or elevated, brownish and purplish, firm, circumscribed nodules made their appearance in the edematous tissue of both lower legs. Small lesions were also present on the soles of the feet. In some areas the lesions were confluent and a hemorrhagic tendency appeared. The clinical appearance was typical of Kaposi's sarcoma and this was confirmed by biopsy of a nodule.

Throughout his course this patient received radiation therapy, a total of 3900 r to the spleen through several portals and 1800 r to the legs. The response was good. The spleen receded to 50 per cent of its original size but became adherent posteriorly and the nodules of the legs were replaced by depressed brown scars. After two-and-one-half years, the patient's general condition was fair. He then developed a nonproductive cough and the edema below the knees was assuming elephantiasic proportions.

The patient died of pneumonia at the Montefiore Hospital and was autopsied. Small Kaposi lesions were found in the lungs, tracheo bronchial lymph nodes and suprarenal cortex. Neither the spleen, inguinal nor pelvic lymph nodes were involved by this process. The cause of the splenomegaly was not definitely determined, though investigation of this point is in progress.

*Case 2. History* (Adm. #454233). The patient, a Russian housewife, aged 67 years, had had dyspnea and precordial pain on exertion for many years. Some years ago ankle and leg edema were first observed. She became bedridden due to progressive dyspnea, weakness and sharp left upper quadrant abdominal pain four months before admission to the Hospital. Blue nodules on her legs were said to be of recent origin.

*Examination.* Clinically, there was a generalized slight enlargement of the superficial lymph nodes. The chest was markedly emphysematous and there was evidence of fluid in both pleural cavity. The size of the heart could not be ascertained. There was a soft blowing basal systolic murmur. The peripheral arteries were thickened. The systolic blood pressure was 130 mm. Hg. and the diastolic 60 mm. Hg. A nodular, fixed, slightly tender mass was felt in the left upper quadrant extending four finger breadths below the costal margin. The liver was not palpable. A pea-sized purple nodule was present near the external urethral meatus. There was diffuse pitting edema of the legs and thighs. Many purple infiltrated nodules up to 3 cm. in diameter were present over both lower extremities. These had the typical appearance of Kaposi's sarcomatous nodules. Edema was also noted in the supraclavicular fossae.

*Laboratory data.* The hemoglobin was 62 per cent (15.5 G. = 100 per cent). The red blood count was 3,890,000 per cu. mm.; the white blood cells numbered 5,200 per cu. mm. and the platelets 100,000 per cu. mm. The hemogram showed segmented neutrophils 18

per cent, non-segmented neutrophils 15 per cent, lymphocytes 50 per cent, monocytes 8 per cent, segmented eosinophils 5 per cent, segmented basophils 2 per cent, plasma cells 2 per cent and reticulocytes 0.5 per cent. Sternal bone marrow obtained by aspiration revealed a normal cellular distribution. There was a trace of albumin in the urine. Occult blood was not found in the examination of one stool specimen. The saccharin circulation time was 17 seconds and the antecubital venous pressure was 7.5 cm. of blood. The bleeding time was two-and-a-half minutes, the coagulation time six minutes and the clot retraction normal. The blood urea N was 11 mg. per cent; the icterus index was 9 and the blood Wassermann test was negative. The electrocardiogram revealed left axis deviation and slight depression of the R-T segment in leads 1 and 2. Roentgenologic study revealed an effusion at the base of each lung. There was a marked density in the upper portion of the cardiac shadow and depression of the left main bronchus. The pelvic and extremity bones were normal.

*Course.* The clinical course was progressively downhill with persistent dyspnea, cyanosis, cough, restlessness and low-grade fever. On several occasions thoracentesis yielded blood-tinged fluid. Before death, biopsies were performed of each leg and an axillary lymph node. Kaposi's sarcoma was found in all the specimens.

*Necropsy findings.* Examination at autopsy revealed moderate dilatation of both the right and left ventricles of the heart. The valves and endocardium showed no abnormalities. The coronary arteries were thickened and their lumina irregularly narrowed by arteriosclerotic plaques. The epicardium was thin and glistening. Two firm bluish nodules, 3 mm. in diameter, were observed through the epicardium near the posterior descending branch of the left coronary artery. A similar nodule was present near the right coronary artery on the anterior surface of the heart. 300 cc. of serosanguinous fluid was found in each pleural cavity. The lungs were moist and congested. The bronchi were injected and the lumina contained moderate amounts of mucoid material. Tumor nodules were not present in the respiratory tract or pleurae. On the left side of the tongue just behind the sulcus terminalis two 2 mm. bluish tumor nodules were observed. A flat tumor nodule, 3 mm. in diameter was present in the submucosa of the greater curvature of the stomach. A few similar nodules were present in the mesentery and in the small intestines at the attached border. Shining through the serosa of the free portion of the small intestines and the large intestines, many pea-sized tumor nodules were observed. These were all situated in the mucosa and submucosa and were covered by intact epithelium. An unexpected finding was an ulcerated, firm, fungating adenocarcinoma of the sigmoid colon. There were no metastases from this lesion. Moderate fatty degeneration of the liver was observed. There was marked enlargement and matting of the hypogastric, preaortic, tracheobronchial, paratracheal, mediastinal and mesenteric lymph nodes. These on section were fleshy or hard and grey to bluish brown. Microscopically they were partially or completely replaced by angiosarcomatous tumor tissue. The spleen weighed 700 grams. The capsule was smooth. On cut surface the organ was found to be soft with easily visible follicles. The trabeculae were not increased. There were several pale, brownish grey, ill-demarcated areas close to the capsule. Microscopic examination revealed tumor tissue in all sections. This consisted primarily of nests of spindle cells and fibrosarcomatous tissue. The vascular and inflammatory elements found in other locations were not prominent. The demarcation between tumor and normal spleen was indistinct. The urinary tract did not reveal significant lesions. In the right broad ligament close to the uterus there were two firm tumor nodules measuring 3 mm. in diameter. Several similar nodules were present in the diaphragm. Examination of the brain revealed an arteriosclerotic encephalopathy.

*Case 3. History* (Adm. #411193).<sup>3</sup> A Russian housewife, aged 43 years, was under observation for eight months until her death. Her illness started eleven years ago with swelling of both legs, which subsided after rest, and a painless, colorless swelling

<sup>3</sup> The latter part of this patient's course was followed in the Montefiore Hospital.

near the right ankle. Three years ago a similar but bluish swelling was observed on the left ankle. Numerous painless, bluish nodules then appeared on the lower extremities. At the same time she experienced widespread spontaneous ecchymoses and developed progressive weakness. Several weeks before coming under observation there was a rapid increase in the size of the lesions on her legs and subcutaneous swellings were noted on each side of the neck.

*Examination.* She exhibited marked anterior and posterior cervical lymphadenopathy. The nodes were discrete, non-tender and freely movable. There was slight axillary lymph node enlargement but the inguinal nodes could not be felt. In the right anterior auricular region a diffuse thickening was apparent. On the posterior lip of the left Eustachian tube there was a small submucosal nodule. Two purplish pea-sized nodules were present on the posterior pharyngeal wall. The spleen was palpable one finger below the costal margin. In the right upper quadrant of the abdomen an elongated, non-tender mass, which may have represented retroperitoneal lymph nodes, was felt. In addition, the skin in this region was moderately thickened. There were several small, freely movable nodules on the posterior rectal wall. Multiple elevated hemorrhagic nodules, typical of Kaposi's sarcoma, were present on the thighs, legs, feet and toes. In addition several flat erythematous areas were present. The legs were swollen to twice normal size and pitted slightly on pressure; above the knees, however, there was no edema whatsoever. The skin of the legs was discolored reddish yellow and seemed infiltrated.

*Laboratory data.* The hemoglobin was 69 per cent (15.5 G. = 100 per cent), the red blood count 4,290,000 per cu. mm.; the white blood count 3,150 per cu. mm. and the platelet count 80,000 per cu. mm. The hemogram showed segmented neutrophils 46 per cent, non-segmented neutrophils 4 per cent, lymphocytes 45 per cent, monocytes 2 per cent, segmented eosinophils 3 per cent and reticulocytes 0.5 per cent. On subsequent examinations a normal leucocyte count was observed and the monocytes were up to 10 per cent. The bleeding time was two-and-one-half minutes; the tourniquet test yielded negative findings; the coagulation time was six minutes and the clot retraction was normal. Stool and urine examinations yielded normal findings. The blood Wassermann and Kahn reactions were negative. Examination of the chemistry of the blood revealed the sugar as 115 mg. per cent, the urea N as 17 mg. per cent, the cholesterol as 235 mg. per cent, the icterus index as 2, the serum albumin was 5.0 G. per cent and the serum globulin as 1.6 G. per cent. There were no intrathoracic abnormalities on roentgenologic examination. Lesions were not observed in the bony pelvis, skull, ribs or shoulders. A gastrointestinal x-ray series was negative. Biopsy of a bluish nodule on the right leg and a cervical lymph node revealed Kaposi's sarcoma (angiomatous fibrosarcoma) in both sections. The operative wounds healed without difficulty.

*Course.* The course was steadily downhill. The patient was essentially afebrile until shortly before death. She lost weight gradually. Large amounts of straw-colored fluid appeared in the right pleural cavity and several thoracenteses were required. There was a gradual enlargement and spread of the Kaposi skin lesions with involvement of the back and the arms. The edema became more marked and spread to the thighs. The legs became elephantiasic. A moderate hypoproteinemia developed at this time; the serum albumin was 3.4 G. per cent and the globulin 0.9 G. per cent. The cervical lymph nodes enlarged progressively so that at the time of death there was the aspect of a "bull neck". An autopsy was not obtained.

*Case 4. History* (Adm. #385819). The patient, an Italian boy, aged 4 years, was one of similar twins. His illness began one year prior to admission to The Mount Sinai Hospital with two "blue spots" on the left leg. Two months before he entered the hospital, firm, painless swellings were observed in both groins.

*Examination.* Clinically, there were two lesions, about 2 cm. in diameter, in the middle third of the left leg; they were purplish, raised and painless. Below the internal malleolus of the right ankle and the external malleolus of the left, there were firm, purplish plaques. The cervical, axillary and inguinal nodes were palpable, and two large, hard nodes were

found in the right inguinal region. Coarse rales and slightly impaired resonance were noted at the base of each lung. The spleen was not palpable. No lesions were found elsewhere.

*Laboratory data.* The blood chemistry was normal. The urine showed a trace of albumin. One of the hemorrhagic nodules on the left leg was removed and showed a "papillary angiomatous tumor with spindle cells," characteristic of Kaposi's hemorrhagic sarcoma.

*Course.* The course of the disease was at first stationary and thereafter declined slowly and progressively. New lesions appeared over various parts of the body. The presence of pulmonary infiltration was confirmed by roentgen examination. After several months in the hospital, the patient died. The clinical aspects of this case have been presented elsewhere in greater detail by Denzer and Leopold (20).

*Necropsy findings.* At autopsy a large number of purple nodules varying in size up to 6 x 4 cm. were found in the scalp and the skin of the abdomen, lower back and lower extremities. The latter were enlarged to one-and-one-half times the normal size because of edema; moderate pitting on pressure was apparent. All of the superficial lymph nodes were enlarged but remained movable and discrete.

The pleural surfaces of the lungs were studied by irregular, flat, hemorrhagic plaques which penetrated the pulmonary parenchyma in some places. In addition several discrete tumor nodules were present in the right upper and left lower lobes. At the hilus of each lung there was a marked condensation and increase in firm, hemorrhagic, neoplastic tissue which invaded both lower lobes. This encased the vessels and bronchi on the one hand and was continuous centripetally with similar tissue in the posterior mediastinum on the other. About 250 cc. of serosanguinous fluid was present in each pleural cavity.

The heart was free of tumor. There was moderate dilatation and hypertrophy of both ventricles. At the base many irregular indurated hemorrhagic areas were observed in the parietal pericardium. The connective tissue of the mediastinum and retroperitoneal areas was largely replaced by hemorrhagic tumor tissue which bound the various structures to one another. The superior vena cava was narrowed by tumor invasion of its wall. The tracheo-bronchial, paratracheal and paraaortic lymph nodes were markedly enlarged, matted and adherent to adjacent structures. There was extension of tumor tissue into and around the suprarenal glands (the left was largely replaced by tumor), pancreas and kidneys while the same process could be traced down the iliac vessels. The mesenteric lymph nodes were enlarged, fleshy and hemorrhagic, but not fused. The involvement was most severe toward the root of the mesentery. Similar changes were apparent in the nodes at the hilus of the liver and spleen. The liver was moderately enlarged. There were no discrete nodules in the organ but distinct enlargement of larger portal areas was apparent. Tumor tissue was observed in these areas; it did not follow the vessels nor did it infiltrate the parenchyma. The spleen was firm and was several times the normal size. The capsule was smooth; the Malpighian follicles were distinct; there were no nodules. There was considerable reticulum cell hyperplasia of the pulp cords and degenerative change were found in the center of many splenic follicles. Many of the reticulum cells were swollen or vacuolated and their nuclei were in varying stages of necrobiosis.

Throughout the gastrointestinal tract—in the greater curvature and fundus of the stomach, duodenum, jejunum, ileum, appendix and colon—purplish, circumscribed, submucosal nodules up to 1.5 cm. in diameter were observed projecting from both the mucosal and serosal surfaces. At the point where the esophagus passed through the diaphragm, there was a condensation of tumor tissue which infiltrated the wall to the mucosal surface. Tumor tissue invaded the kidneys at the hilus, accompanying the large vessels. In addition a few flat plaques were apparent under the capsule. Tumor was not observed in several sections of ribs and vertebrae; the cellular distribution in the marrow was essentially normal.

Microscopic examination of the tumor in all the regions noted above revealed a varying picture in which bands of collagenous tissue were separated by tumor masses consisting of dilated and malformed "back to back" capillaries, nests of endothelial cells, hemorrhage hemosiderin pigmentation and lymphocytic infiltration. In some areas, especially in the



lungs, invasion of veins could be observed. In lymph nodes it was apparent that tumor strands accompanied the vessels into the hilus.

#### SUMMARY

The visceral manifestations of Kaposi's sarcoma have been described. Particular attention has been directed to the alterations in the lymph nodes, spleen, heart and gastrointestinal and respiratory tracts. The frequent occurrence of edema of the extremities in this disease has been stressed. Four case reports of widespread visceral involvement with Kaposi's sarcoma, including autopsy examination in three, are presented.

#### BIBLIOGRAPHY

1. KAPOSI, M.: Quoted by Kren, O., reference 6.
2. DÖRFFEL, J.: Histogenesis of Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi, *Arch. Dermat. & Syph.*, 26: 608, 1932.
3. CHOISSE, R. M., AND RAMSEY, E. M.: Angioreticuloendothelioma (Kaposi's Disease) of the Heart, *Am. J. Path.*, 15: 155, 1939.
4. MACKEE, G. M., AND CIPOLLARO, A. C.: Idiopathic Multiple Hemorrhagic Sarcoma (Kaposi), *Am. J. Cancer*, 26: 1, 1936.
5. DALLA FAVERA, G. B.: Über das sog. Sarcoma Idiop. Multiplex Haemorrhagicum (Kaposi), *Arch. f. Dermat. u. Syph.*, 109: 387, 1911.
6. KREN, O.: Sarcoma Idiopathicum Haemorrhagicum (Kaposi), in *Handbuch der Haut- und Geschlechtskrankheiten*, J. Jadassohn, Berlin, Julius Springer, 1933, Band 12, Teil 3, p. 891.
7. AEGERTER, E. E., AND PEALE, A. R.: Kaposi's Sarcoma, *Arch. Path.*, 34: 413, 1942.
8. BILANCIONI, G.: Sarcoma di Kaposi con Manifestazioni Faringolaringee, *Rassegna internaz. di clin. e terrap.*, 13: 1135, 1932.
9. USSEGLIO, G., ZAMBELLI, E., AND PAOLINO, W.: Espressioni Biochimiche Sanguigne in un Caso di Morbo di Kaposi, *Gior. d. r. Accad. di med. di Torino*, 101: 404, 1938.
10. DECKER, S. W., AND THATCHER, H. W.: Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi, *J. Invest. Dermat.*, 1: 379, 1938.
11. LANE, C. G., AND GREENWOOD, A. M.: Lymphoblastoma (Mycosis Fungoides) and Hemorrhagic Sarcoma of Kaposi in the Same Person, *Arch. Dermat. & Syph.*, 27: 643, 1933.
12. GOLDSCHLAG, F.: Über einen Fall von Sarcoma Idiopathicum Haemorrhagicum Kaposi mit ungewöhnlichem Vorstadium, *Dermat. Wehschr.*, 100: 204, 1935.
13. COLE, H. N., AND CRUMP, E. S.: Report of 2 cases of Idiopathic Hemorrhagic Sarcoma (Kaposi), the first complicated with Lymphatic Leukemia, *Arch. Dermat. & Syph.*, 1: 283, 1920.
14. SYMMERS, D.: Kaposi's Disease, *Arch. Path.*, 32: 764, 1941.
15. ORMSBY, O. S., AND MONTGOMERY, H.: *Diseases of the Skin*, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 799.
16. DILLARD, G. J., AND WEIDMAN, F. D.: Multiple Hemorrhagic Sarcoma of Kaposi, *Arch. Dermat. & Syph.*, 11: 203, 1925.
17. MIERZECKI, H.: Sarcoma Idiopathicum Multiplex Kaposi, *Arch. f. Dermat. u. Syph.*, 165: 577, 1932.
18. HANSSON, C. J.: Kaposi's Sarcoma, *Acta Radiol.*, 21: 457, 1940.
19. ANDREWS, G. C.: *Diseases of the Skin*, ed. 2, Philadelphia, W. B. Saunders Co., 1939, p. 756.
20. DENZER, B. S., AND LEOPOLD, H. C.: Idiopathic Hemorrhagic Sarcoma (Kaposi), *Am. J. Dis. Child.*, 52: 1139, 1936.



21. GREPPI, E., AND BETTONI, I.: Splenomegalia Emolitica ed Angio-endotheliona Cutaneo Tipo Kaposi con Associazione di Agranulocitosi e Sepsi Orale, Arch. Ist. biochim. ital., 4: 403, 1932.
22. PAOLIMI, R.: Sul Sarcoma Molteplice Primitivo di Kaposi con Speciale riguardo alle Localizzazioni Viscerali, Rassegna internaz. di clin. e terap., 8: 514, 1927.
23. BERTACCINI, G.: Ancora Sulla Sarcomatosi Cutanea di Kaposi (Angio-endotelioma cutaneo di Radaeli), Gior. ital. di dermat. e sif., 80: 631, 1939.
24. WELLER, G. L.: The Clinical Aspects of Cardiac Involvement (Right Auricular Tumor) in Idiopathic Hemorrhagic Sarcoma (Kaposi's Disease), Ann. Int. Med., 14: 314, 1940.
25. CUNHA MOTTA, L.: Hemangio Reticulo-Endotelioma, An. Fac. de med. da Univ. de São Paulo, 17: 627, 1941.
26. HAMILTON-PATERSON, J. L., AND CASTLEDEN, L. I. M.: Intracardiac Tumors, Brit. Heart J., 4: 103, 1942.
27. VAN CLEVE, J. V., AND HELLWIG, C. A.: A Case of Idiopathic Hemorrhagic Sarcoma (Kaposi) with Autopsy Findings, Urol. & Cutan. Rev., 39: 246, 1935.
28. ELJASZ, A.: Über einen Fall vom Kaposi-Sarkom mit Harthormartiger Bildung und Blasentumor, Arch. f. Dermat. u. Syph., 164: 650, 1932.
29. SCHIRMUNSKAJA, K., AND TSCHOTSCHIA, K.: Ein Fall von Idiopathischem Multiplem hamorrhagischem Hautsarkom Kaposi und dessen Röntgenbehandlung, Dermat. Wehnschr., 94: 705, 1932.
30. KUSNEZOW, W. N.: A Case of Sarcoma Multiplex Idiopathicum (Kaposi) with Fatal Outcome, Urol. & Cutan. Rev., 37: 230, 1933.
31. PHILIPPSON, L.: Ueber das Sarcoma Idiopathicum Cutis Kaposi, Virchows Arch. f. path. Anat., 167: 58, 1902.

## EFFECT OF WEIGHT REDUCTION ON COURSE OF ARTERIAL HYPERTENSION<sup>1</sup>

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Hypertension has been found to be three to six times as frequent in obese men and women as in individuals of normal weight (1). Reduction of weight is frequently associated with a decrease of blood pressure, especially in patients with moderate hypertension (2), and affects, to a greater extent, the systolic than the diastolic blood pressure (3). Even in persons of normal weight, weight reduction may lower the blood pressure (4).

This study surveys a group of one hundred and thirty patients with obesity and hypertension who were observed at the Nutrition Clinic of The Mount Sinai Hospital. All had a thorough physical examination, urinalysis and, in many instances, an electrocardiogram, basal metabolism and fluoroscopy. Height, weight, actual and ideal, were determined. Patients with clinical signs of heart failure, kidney disease or electrocardiographic evidence of myocardial damage were excluded.

Special attention was paid to the ocular changes in a group of twenty-two patients; the fundi of these cases were examined by one of us and followed up at intervals. Individuals with myopia were excluded.

The treatment of obesity consisted of a low calorie diet (1200 calories) with an adequate supply of proteins, vitamins and minerals. In this group no medication, dehydrating measures or thyroid were used. The patients were seen at the clinic at one to two week intervals. On each occasion body weight and blood pressure were determined, the latter always by the same examiner and with the patient seated.

### FIRST SURVEY: 1940-1941

Of the original series of one hundred and thirty patients, seventy-six had to be excluded because of irregular visits to the clinic, lack of cooperation and inability to adhere to the prescribed regimen. The remaining 54 patients are the subject of the following analysis.

The age of this group varied from 33 to 68 years; the average was  $53\frac{1}{2}$  years. The initial weight ranged from 148 to 284 pounds; the weight after the accomplished weight reduction (final weight) 115 to 249 pounds. The ideal weight ranged between 120 to 158 pounds. All patients had various degrees of arterial hypertension. Systolic blood pressures over 140 mm. Hg and diastolic blood pressure over 85 were considered abnormal. These cases were treated and followed up over a period of 1 to 19 months (June, 1940-December, 1941; average 8.2 months), during which time a loss of weight from 9 to 80 pounds occurred (average  $23\frac{1}{2}$  pounds). The loss of weight was associated with a decreased blood pressure in 39 patients (72%), while in 15 patients (28%) no change in

<sup>1</sup> From The Nutrition Clinic, The Medical Services, and The Eye Service of The Mount Sinai Hospital, New York.

TABLE 1  
*Essential data of 39 patients of group I*  
 Weight reduction resulted in a lowering of blood pressure

| CASE NO. | AGE | SEX | ID. WT. | FIRST EXAMINATION |                   |         | LAST EXAMINATION |                   |         | RESULTING CHANGES |        |        | DUR. TR. |
|----------|-----|-----|---------|-------------------|-------------------|---------|------------------|-------------------|---------|-------------------|--------|--------|----------|
|          |     |     |         | Date              | Wt.               | B.P.    | Date             | Wt.               | B.P.    | Wt.               | S.B.P. | D.B.P. |          |
|          |     |     |         | lbs.              | lbs.              | mm. Hg  |                  | lbs.              | mm. Hg  | lbs.              | mm. Hg | mm. Hg | mos.     |
| 7*       | 60  | f   | 138     | 6-7-40            | 173 $\frac{3}{4}$ | 190/120 | 10-24-41         | 151 $\frac{1}{2}$ | 165/100 | -22               | -25    | -20    | 17       |
| 4        | 50  | f   | 120     | 6-5-40            | 135 $\frac{1}{2}$ | 170/80  | 9-29-41          | 125 $\frac{1}{2}$ | 130/80  | -10               | -40    | 0      | 15       |
| 8        | 47  | f   | 130     | 5-27-40           | 163 $\frac{1}{2}$ | 140/95  | 4-18-41          | 138 $\frac{1}{4}$ | 120/80  | -25               | -20    | -15    | 11       |
| 12       | 44  | f   | 158     | 6-12-40           | 250 $\frac{1}{2}$ | 150/90  | 12-27-40         | 216 $\frac{1}{2}$ | 108/70  | -34               | -42    | -20    | 7        |
| 13*      | 64  | m   | 144     | 6-14-40           | 272 $\frac{1}{2}$ | 185/110 | 6-23-41          | 193 $\frac{1}{4}$ | 108/72  | -80               | -77    | -38    | 12       |
| 18*      | 55  | f   | 129     | 6-19-40           | 158 $\frac{1}{2}$ | 182/106 | 10-11-40         | 149 $\frac{1}{2}$ | 154/90  | -9                | -28    | -16    | 5        |
| 20       | 61  | f   | 125     | 6-19-40           | 157 $\frac{1}{2}$ | 145/90  | 6-16-41          | 135               | 122/70  | -23               | -23    | -20    | 12       |
| 25       | 51  | f   | 129     | 6-28-40           | 154               | 220/130 | 9-18-40          | 140 $\frac{1}{2}$ | 176/120 | -14               | -44    | -10    | 3        |
| 27       | 57  | f   | 153     | 7-8-40            | 228 $\frac{1}{2}$ | 198/98  | 9-10-41          | 200 $\frac{1}{2}$ | 140/75  | -28               | -58    | -23    | 14       |
| 33       | 62  | f   | 129     | 7-19-40           | 164               | 220/110 | 9-13-40          | 153 $\frac{1}{2}$ | 194/100 | -11               | -26    | -10    | 2        |
| 41       | 51  | f   | 137     | 8-19-40           | 212 $\frac{1}{2}$ | 178/100 | 11-25-40         | 195               | 156/90  | -17               | -22    | -10    | 3        |
| 44       | 51  | f   | 126     | 8-23-40           | 159               | 232/130 | 1-3-41           | 144 $\frac{1}{4}$ | 212/138 | -15               | -20    | +8     | 4        |
| 48       | 57  | f   | 138     | 9-9-40            | 159 $\frac{1}{2}$ | 220/110 | 4-16-41          | 144 $\frac{1}{2}$ | 192/100 | -15               | -28    | -10    | 7        |
| 56*      | 48  | f   | 130     | 9-27-40           | 152 $\frac{1}{2}$ | 225/110 | 1-29-41          | 139               | 178/100 | -14               | -47    | -10    | 4        |
| 60*      | 52  | f   | 141     | 10-11-40          | 284               | 148/96  | 9-29-41          | 248 $\frac{3}{4}$ | 130/80  | -35               | -18    | -16    | 12       |
| 61       | 49  | f   | 141     | 9-30-40           | 216               | 170/100 | 2-28-41          | 172               | 148/110 | -44               | -22    | +10    | 5        |
| 63       | 38  | m   | 152     | 9-23-40           | 273 $\frac{1}{2}$ | 156/110 | 12-20-40         | 245 $\frac{1}{2}$ | 145/100 | -28               | -11    | -10    | 3        |
| 82       | 50  | f   | 148     | 12-2-40           | 211 $\frac{1}{2}$ | 170/100 | 2-20-41          | 197               | 155/90  | -15               | -15    | -10    | 3        |
| 83*      | 55  | f   | 131     | 12-13-40          | 187 $\frac{1}{4}$ | 185/105 | 12-29-41         | 167 $\frac{1}{2}$ | 160/80  | -20               | -25    | -25    | 12       |
| 85       | 59  | f   | 144     | 12-16-40          | 196               | 192/110 | 10-24-41         | 170 $\frac{1}{2}$ | 172/100 | -26               | -20    | -10    | 10       |
| 89*      | 51  | f   | 135     | 11-18-40          | 147               | 170/100 | 12-24-41         | 135 $\frac{1}{4}$ | 144/100 | -12               | -26    | 0      | 13       |
| 91*      | 47  | f   | 124     | 12-9-40           | 137               | 215/110 | 6-27-41          | 115 $\frac{1}{4}$ | 174/95  | -22               | -41    | -15    | 7        |
| 93       | 53  | m   | 142     | 1-10-41           | 190               | 190/120 | 9-6-41           | 163 $\frac{1}{2}$ | 155/95  | -27               | -35    | -25    | 8        |
| 94       | 47  | f   | 137     | 1-10-41           | 153               | 208/120 | 10-10-41         | 135               | 150/90  | -18               | -58    | -30    | 9        |
| 97       | 68  | f   | 133     | 1-6-41            | 182 $\frac{1}{2}$ | 200/100 | 5-21-41          | 155               | 172/80  | -27               | -28    | -20    | 5        |
| 98*      | 47  | f   | 141     | 2-10-41           | 166               | 186/110 | 12-24-41         | 141 $\frac{3}{4}$ | 167/100 | -24               | -19    | -10    | 11       |
| 99       | 51  | f   | 141     | 1-15-41           | 148               | 170/100 | 10-29-41         | 138 $\frac{3}{4}$ | 155/90  | -9                | -15    | -10    | 10       |
| 101*     | 47  | f   | 133     | 2-10-41           | 185 $\frac{1}{2}$ | 218/140 | 12-24-41         | 169               | 172/100 | -17               | -46    | -40    | 10       |
| 103      | 52  | f   | 133     | 2-21-41           | 150 $\frac{1}{2}$ | 172/100 | 6-6-41           | 136               | 128/80  | -14               | -44    | -20    | 4        |
| 107*     | 50  | f   | 133     | 4-2-41            | 155 $\frac{1}{2}$ | 210/115 | 12-29-41         | 145 $\frac{1}{4}$ | 182/100 | -10               | -28    | -15    | 9        |
| 108*     | 44  | f   | 130     | 4-30-41           | 145               | 160/100 | 9-24-41          | 129               | 150/90  | -16               | -10    | -10    | 5        |
| 109      | 53  | f   | 133     | 4-11-41           | 192               | 190/110 | 10-13-41         | 155 $\frac{1}{2}$ | 175/100 | -37               | -15    | -10    | 6        |
| 110      | 56  | f   | 131     | 3-7-41            | 214 $\frac{1}{2}$ | 200/120 | 9-26-41          | 178               | 165/90  | -37               | -35    | -30    | 7        |
| 111*     | 42  | f   | 150     | 5-19-41           | 226 $\frac{1}{2}$ | 190/120 | 12-29-41         | 180 $\frac{1}{2}$ | 178/100 | -46               | -12    | -20    | 7        |
| 112*     | 65  | f   | 145     | 3-21-41           | 200               | 218/120 | 12-26-41         | 176 $\frac{1}{4}$ | 178/100 | -24               | -40    | -20    | 9        |
| 115*     | 33  | f   | 127     | 5-7-41            | 215 $\frac{1}{2}$ | 205/100 | 12-26-41         | 171               | 142/78  | -45               | -63    | -22    | 8        |
| 117      | 58  | m   | 153     | 4-21-41           | 222               | 178/110 | 9-24-41          | 202               | 140/80  | -20               | -38    | -30    | 5        |
| 119      | 54  | m   | 158     | 4-2-41            | 172               | 193/135 | 6-16-41          | 161 $\frac{1}{2}$ | 160/100 | -11               | -33    | -35    | 3        |
| 121      | 66  | f   | 127     | 6-25-41           | 156               | 185/80  | 10-28-41         | 141               | 155/75  | -15               | -30    | -5     | 4        |

Abbreviations used in Tables 1-4: B.P.—Blood pressure; D.B.P.—Diastolic blood pressure; Dur.Tr.—Duration of treatment; Id.Wt.—Ideal weight; S.B.P., Systolic blood pressure; Wt.—Weight.

\* For changes in the fundi in this case see table 5.

blood pressure was observed. The two groups are presented in tables 1 and 2. Comparison of group I and II reveals the following data:

Group I consists of 6 male and 33 female patients, group II of 1 male and 14 females. Thus, females represent the great majority, which fact may perhaps be explained by the analogous relationship of both sexes in the clinic population. There is practically no difference in the age factor in both groups; the average age is 53 for group I and 54 for group II. Nor is there an obvious difference in the ideal weight of the groups (137 lbs. and 135 lbs., respectively). The initial weight averaged 187 pounds in group I and 175 pounds in group II. The higher weight average of group I is caused by a single case (No. 13) whose

TABLE 2  
*Essential data of 15 cases of group II*  
Weight reduction did not affect the blood pressure

| CASE NO. | AGE | SEX | ID. WT. | FIRST EXAMINATION |      |         | LAST EXAMINATION |      |         | RESULTING CHANGES |        |        | DUR. TR. |
|----------|-----|-----|---------|-------------------|------|---------|------------------|------|---------|-------------------|--------|--------|----------|
|          |     |     |         | Date              | Wt.  | B.P.    | Date             | Wt.  | B.P.    | Wt.               | S.B.P. | D.B.P. |          |
|          |     |     |         | lbs.              | lbs. | mm. Hg  |                  | lbs. | mm. Hg  | lbs.              | mm. Hg | mm. Hg | mos.     |
| 11*      | 54  | m   | 144     | 6-12-40           | 162  | 170/80  | 4-11-41          | 145½ | 160/90  | -16               | -10    | +10    | 10       |
| 29*      | 49  | f   | 135     | 7-8-40            | 179½ | 175/105 | 9-29-41          | 145½ | 174/100 | -34               | -1     | -5     | 15       |
| 54*      | 56  | f   | 133     | 10-23-40          | 162  | 210/140 | 5-7-41           | 130  | 220/120 | -32               | +10    | -20    | 7        |
| 69       | 45  | f   | 132     | 10-7-40           | 186  | 220/120 | 8-16-41          | 160½ | 220/100 | -26               | 0      | -20    | 10       |
| 70*      | 59  | f   | 129     | 11-3-40           | 163  | 245/135 | 10-24-41         | 129  | 238/130 | -34               | -7     | -5     | 12       |
| 75       | 50  | f   | 138     | 11-15-40          | 202½ | 258/140 | 5-5-41           | 166  | 250/150 | -36               | -8     | +10    | 6        |
| 87       | 65  | f   | 125     | 12-18-40          | 177½ | 220/110 | 6-2-41           | 156½ | 230/110 | -21               | +10    | 0      | 6        |
| 100*     | 48  | f   | 130     | 2-17-41           | 147½ | 160/100 | 12-24-41         | 132½ | 180/100 | -15               | +20    | 0      | 10       |
| 105*     | 62  | f   | 141     | 2-19-41           | 190  | 180/115 | 12-26-41         | 160½ | 188/110 | -30               | +8     | -5     | 10       |
| 106      | 55  | f   | 138     | 2-26-41           | 160  | 186/120 | 12-22-41         | 143  | 178/95  | -17               | -8     | -25    | 10       |
| 116*     | 61  | f   | 131     | 5-5-41            | 164½ | 205/110 | 12-29-41         | 143½ | 215/100 | -22               | +10    | -10    | 8        |
| 126      | 51  | f   | 141     | 2-10-41           | 159  | 184/115 | 10-20-41         | 134½ | 176/110 | -25               | -8     | -5     | 8        |
| 129*     | 40  | f   | 129     | 10-22-41          | 219½ | 180/120 | 12-29-41         | 200½ | 180/128 | -19               | 0      | +8     | 2        |
| 120      | 56  | f   | 135     | 5-14-41           | 192  | 170/100 | 6-18-41          | 183½ | 188/85  | -9                | +18    | -15    | 1        |
| 122      | 52  | f   | 138     | 3-19-41           | 154  | 180/110 | 9-24-41          | 143  | 184/110 | -11               | +4     | 0      | 6        |

initial weight was 284 pounds. The final weight of group I averaged 162 pounds as compared with 152 pounds in group II. The average weight loss was 24 pounds in group I and 23 pounds in group II. In other words, the loss of weight was almost identical in both groups.

What was the result of the weight reduction on the systolic and diastolic blood pressure in these two groups?

Group I, as a whole, presents from the beginning, moderately lower levels of both systolic and diastolic blood pressure. The average blood pressure for group I was systolic 188 mm. Hg, diastolic 109; for group II systolic 196, diastolic 114.

In the course of observation a considerable drop in the systolic and diastolic blood pressure occurred in group I. The average reduction was 32 mm. Hg in the systolic and 16 mm. Hg in the diastolic blood pressure.

In contrast to group I, there was no change in the blood pressure levels of group II (see table 3). The average systolic blood pressure rose slightly from 196 to 198 mm. Hg and the diastolic, which had been 114 at the beginning, was 110 mm. Hg at the end of the observation period. It is not likely that the somewhat longer duration of treatment of group I (average 8.8 months versus 8.1 months) was responsible for the better result in group I. The impression was rather that in group II we were dealing from the beginning with a somewhat severer form of hypertension which failed to be lowered by weight reduction. Interestingly enough, both groups showed remarkable subjective improvement after weight reduction. The patients were able to walk longer distances without

TABLE 3  
*Comparison of data of groups I and II*

|                                     | GROUP I (39 PATIENTS)—RANGE OF VARIATION |     |         | GROUP II (15 PATIENTS)—RANGE OF VARIATION |     |         |
|-------------------------------------|--|-----|---------|---|-----|---------|
|                                     | From                                     | To  | Average | From                                      | To  | Average |
| Age (years).....                    | 33                                       | 68  | 53      | 40  | 65  | 54      |
| Ideal weight (lbs.).....            | 120                                      | 158 | 137     | 125                                       | 144 | 135     |
| Initial weight (lbs.).....          | 148                                      | 284 | 187     | 148                                       | 220 | 175     |
| Final weight (lbs.).....            | 115                                      | 249 | 162     | 129                                       | 201 | 152     |
| Initial systolic B.P. (mm. Hg)      | 140                                      | 232 | 188     | 160                                       | 258 | 196     |
| Final systolic B.P. (mm. Hg)        | 108                                      | 212 | 157     | 160                                       | 250 | 198     |
| Initial diastolic B.P. (mm. Hg)     | 80                                       | 140 | 109     | 80  | 140 | 114     |
| Final diastolic B.P. (mm. Hg)       | 70                                       | 138 | 92      | 85  | 150 | 110     |
| Loss of weight (lbs.).....          | 9  | 80  | 24      | 9   | 36  | 23      |
| Drop of systolic B.P. (mm. Hg)      | 10                                       | 77  | 32      | -10                                       | +20 | +3      |
| Drop of diastolic B.P. (mm. Hg)     | 0  | 38  | 16      | -20                                       | +10 | -5      |
| Duration of treatment (months)..... | 2  | 17  | 8.8     | 1   | 15  | 8.1     |

shortness of breath, and were less easily fatigued. Those who complained of headaches and dizziness reported great improvement or disappearance of these symptoms, especially in group I.

The pathological findings in the fundi did not permit a differentiation between group I and II. The severity of the vascular-ocular changes were practically identical in both groups, (see "Evaluation of Changes in the Fundi").

#### SECOND SURVEY: 1944

A comparatively small group of patients was rechecked after an interval of three years. Due to various conditions beyond our control only 15 patients of the original 53 were available for study. Although this number is small, the results of the check-up presented some interesting features.

All 15 patients had lost weight during the original observation period which



lasted from June, 1940 to December, 1941; the average loss of weight in these patients had been 24.7 pounds.

After three years, three patients had maintained their weight at the reduced level (nos. 20, 70, 89), three others continued to lose weight (nos. 7, 13, 120), while nine patients regained weight (nos. 4, 11, 18, 44, 56, 60, 91, 98, 101) (table 4). In other words, 60 per cent of the follow-up cases failed to maintain the reduced weight level.

What was the effect on the blood pressure?

Of the three patients who maintained the reduced weight level, two showed a persistently lower blood pressure, while one exhibited a moderate increase.

TABLE 4

*Comparison of findings in 1940-1941 and in 1944 in a group of 15 cases*

| CASE NO. | FINDINGS IN 1940-1941 |                   |               |               | FINDINGS IN 1944  |               |
|----------|-----------------------|-------------------|---------------|---------------|-------------------|---------------|
|          | Weight                |                   | B.P.          |               | Weight            | B.P.          |
|          | Initial               | Final             | Initial       | Final         |                   |               |
|          | <i>lbs.</i>           | <i>lbs.</i>       | <i>mm. Hg</i> | <i>mm. Hg</i> | <i>lbs.</i>       | <i>mm. Hg</i> |
| 4        | 135 $\frac{3}{4}$     | 125 $\frac{1}{2}$ | 170/ 80       | 130/ 80       | 148 $\frac{1}{2}$ | 155/ 80       |
| 7        | 173 $\frac{3}{4}$     | 151 $\frac{1}{2}$ | 190/120       | 165/100       | 147               | 180/100       |
| 11       | 162                   | 145 $\frac{3}{4}$ | 170/ 80       | 160/ 90       | 162               | 212/100       |
| 13       | 272 $\frac{3}{4}$     | 193 $\frac{1}{4}$ | 185/ 80       | 108/ 72       | 183               | 105/ 60       |
| 18       | 158 $\frac{1}{2}$     | 149 $\frac{1}{2}$ | 182/106       | 154/ 90       | 169 $\frac{1}{2}$ | 164/100       |
| 20       | 157 $\frac{3}{4}$     | 135               | 145/ 90       | 135/ 70       | 141 $\frac{1}{2}$ | 120/ 70       |
| 44       | 159                   | 144 $\frac{1}{2}$ | 232/130       | 212/138       | 162 $\frac{1}{2}$ | 185/138       |
| 56       | 152 $\frac{3}{4}$     | 139               | 225/110       | 178/100       | 150 $\frac{1}{2}$ | 210/110       |
| 60       | 284                   | 248 $\frac{3}{4}$ | 148/ 96       | 130/ 80       | 288               | 130/ 80       |
| 70       | 163                   | 129               | 245/135       | 238/130       | 135 $\frac{1}{4}$ | 195/110       |
| 89       | 147                   | 135 $\frac{1}{4}$ | 170/100       | 144/100       | 137               | 160/ 95       |
| 91       | 137                   | 115 $\frac{1}{4}$ | 215/110       | 174/ 95       | 123               | 204/110       |
| 98       | 166                   | 141 $\frac{1}{4}$ | 186/110       | 167/100       | 151               | 162/100       |
| 101      | 185 $\frac{1}{2}$     | 169               | 218/140       | 172/100       | 182 $\frac{1}{2}$ | 170/100       |
| 120      | 192                   | 183 $\frac{1}{2}$ | 170/100       | 188/ 85       | 154 $\frac{1}{2}$ | 155/ 90       |

Of the three patients who continued to lose weight during the following 3 year interval, the blood pressure remained low in 1 case, showed an additional drop in another and rose in the third.

In the group of nine cases who regained weight during this time, 5 showed a considerable rise in blood pressure, two were unchanged and two exhibited a moderate decrease.

It may be concluded that during the 3-year follow-up, the course of the hypertension was more favorable in patients who maintained their weight at reduced levels than in those who gained. Great caution is necessary in evaluating therapeutic results as individual factors are important. It may happen that the blood pressure may rise despite maintenance of a reduced weight or that, *vice versa*, despite an increased weight, the blood pressure may decrease. Apparently, overweight—as age, diet and other factors—is only a “conditioning influence upon the development of hypertension” (4).

TABLE 5  
*Changes in the fundi*

| CASE NO. | FINDINGS IN 1940-1941   | FINDINGS IN 1944  | COMMENT  |
|----------|---|---|--|
| 7        | 1/24/41—Slight straightening of arterioles. No compression.<br><br>10/24/41—Calibre of vessels same. Questionable compression.                        | 11/2/44—Arterioles moderately narrowed and straightened. No compression.  | No demonstrable change in vessels of fundi.  |
| 11       | 11/8/40—Arteries and veins moderately narrowed and straightened with attenuation in periphery.  | 11/20/44—Somewhat increased light reflex on arteries. Calibre and course of vessels unchanged.                                    | No change in fundus vessels.   |
| 13       | 10/20/40—Arterial twigs at macula tortuous. Slight arterio-venous compression.<br><br>10/10/41.—Same.   | 11/6/44—Decreased light reflex on arteries. Twigs at macula tortuous. No arterio-venous compression.                              | Loss of arterio-venous compression but no change in vessel calibre or tortuosity.        |
| 18       | 10/11/40—Ratio of calibre of veins to arteries 2 to 1. Some straightening. One area of arterio-venous compression in O.S.<br><br>12/24/41.—No change. | 11/2/44—Beginning increase in light reflex on arteries. No other change in vessels but area of arterio-venous compression absent. | Loss of arterio-venous compression but no change in vessel calibre or course of vessels. |
| 29       | 12/20/40—Arteries and veins both very narrow and somewhat straightened.<br>10/10/41—No change.  |   | No change in fundus vessels.   |
| 54       | 12/20/40—Arteries and veins narrowed and straightened with increased light reflex.<br>5/16/41—Same.   |   | No change in fundus vessels.   |
| 56       | 10/11/40—Increased reflex on arteries.<br>12/24/41—Moderately increased light reflex. Some straightening in periphery.                                | 11/2/44—Same.   | No change in fundus vessels.   |
| 60       | 10/25/40—Some straightening of arteries in periphery with increased reflex on arteries.<br>11/7/41—No change.   | 11/2/44—Arterioles somewhat narrowed and straightened. No compression.  | No change.   |

TABLE 5—*Continued*

| CASE NO. | FINDINGS IN 1940-1941   | FINDINGS IN 1944   | COMMENT  |
|----------|---|--|--|
| 70       | 2/21/41—Increased light reflex on arteries.<br>10/24/41—Light reflex increased. Some narrowing of arterioles in periphery.  | 11/16/44—Increased light reflex on arteries. No compression. Ratio of calibre of veins to arteries 3 to 1. Some pigment absorption at maculae. | Increase in changes in retinal vessels with resultant early degeneration at maculae. |
| 83       | 12/20/40—Slightly increased reflex on arteries.<br>12/29/41—Moderate narrowing and straightening of arteries.   |  | About the same.  |
| 89       | 2/7/41—Arterioles moderately straightened and narrowed.<br>12/24/41—Same.   | 11/9/44—No change.   | No change.   |
| 91       | 1/24/41—Arterioles good calibre but somewhat straightened.<br>5/2/41—Moderately increased light reflex on arteries.   | 11/2/44—Arterioles moderately narrowed and straightened.   | Slight advance in vessel narrowing.  |
| 98       | 5/20/41—Arterioles moderately narrowed with slight arterio-venous compression.<br>12/24/41.—Same.   | 11/2/44—Vessels same but arterio-venous compression absent.  | Loss of arterio-venous compression.  |
| 100      | 3/21/41—Arteries and veins somewhat attenuated and straightened.<br>12/24/41—No change.   |  | No change.   |
| 101      | 2/21/41—Disc margins blurred O.U. Veins engorged. Arterioles narrowed. Some arterio-venous compression.<br>12/24/41—Disc margins clear. No exudates or hemorrhages. Vessel calibre unchanged. | 11/6/44—Disc margins clear. Arterioles quite narrowed. Occasional arterio-venous compression. No exudates or hemorrhages.                      | Disappearance of exudates and disc margin blurring. Vessel narrowing unaffected.     |
| 105      | 3/21/41—Arterioles quite narrow with irregularity of calibre. No compression.<br>12/26/41—Same.   |  | No change.   |
| 107      | 4/4/41—Arterioles moderately narrowed. Arteries and veins straightened.   |  | About the same.  |

TABLE 5—*Concluded*

| CASE NO. | FINDINGS IN 1940-1941   | FINDINGS IN 1944 | COMMENT            |
|----------|---|------------------|--------------------|
|          | 12/29/41—As above, with possibly some arterio-venous compression.   |                  |                    |
| 108      | 5/2/41—Some narrowing and straightening in periphery.<br>9/26/41—Same.  |                  | No change.         |
| 111      | 6/6/41—Vessels quite narrowed and straightened throughout fundi.<br>12/29/41—Same.  |                  | No change.         |
| 112      | 5/18/41—Moderately increased reflex on arteries with narrowing of vessels in periphery.<br>12/26/41—Vessels same with early arterio-venous compression. |                  | Vessels unchanged. |
| 115      | 5/16/41—Slight narrowing of vessels in periphery with increased reflex on arteries.<br>12/26/41—Same.   |                  | No change.         |
| 116      | 5/16/41—Arterio-venous compression moderate with narrowing and straightening of vessels present.<br>12/17/41—Same.                                      |                  | No change.         |
| 129      | 10/24/41—Arterioles moderately narrowed and straightened.<br>No compression.<br>12/29/41—No change.   |                  | No change.         |

## EVALUATION OF CHANGES IN THE FUNDI

The disappearance and appearance of exudates, degenerative lesions, hemorrhages and edema of the nerve head margins are easily ascertained and noted. However, when it comes to vessel calibre, or degree of tortuosity, or straightening of an arteriole or venule, or very early compression or displacement of a vein at an arterio-venous crossing, it is extremely difficult to be certain that changes have or have not taken place unless they are very pronounced. In cases 13, 18 and 98, the arterio-venous compression disappeared but it was not pronounced when first noted. In cases 70 and 91, there was gradual decrease in the calibre of the arterioles with resultant changes of degeneration of the maculae in case 70. In case 101, the exudates and the edema of the disc margins disappeared but the calibre of the vessels did not improve.

It is interesting to note that the fundus changes which can improve are hemorrhages, exudates, edema of the nerve head and early arterio-venous compression. These are identical with the changes that are noted in patients who have had operative interference for hypertension. The changes in the blood vessels seem to be irreversible and may continue to deteriorate as in cases 70 and 91.

#### SUMMARY

1. The result of weight reduction on the course of arterial hypertension was studied in a group of fifty-four patients in the years 1940-1941. The average course of dietary treatment was 8.2 months; the average loss of weight during this period was  $23\frac{1}{2}$  pounds. The loss of weight was associated with a decreased blood pressure in 72 per cent and with no change of blood pressure in 28 per cent of the cases.

2. Fifteen patients of the original group were re-examined in 1944. With due consideration of individual variations, the course of arterial hypertension was more favorable in those who maintained their weights at reduced levels than in those who increased in weight during the 3 year interval. Overweight is apparently only one of many conditioning factors for the development of arterial hypertension.

3. Loss of weight and the return of blood pressure to lower or normal levels had practically no effect on the vascular changes of the fundi.

#### BIBLIOGRAPHY

- (1) ROBINSON, S. C., M. BRUCER AND J. MOSS: *J. Lab. & Clin. Med.*, 25: 807, 1940.
- (2) JOHN, H. J.: *Endocrinology*, 13: 388, 1929.
- (3) PREBLE, W. E.: *Boston Med. & Surg. J.*, 188: 617, 1923.
- (4) MOSHCOWITZ, E.: *J. Mt. Sinai Hosp.*, 11: 357, 1945.



# CANCER OF THE LUNG IN THE PRESENCE OF PULMONARY TUBERCULOSIS\*

## REPORT OF TWO CASES

H. HENNEL, M.D.

*Case 1. History.* The first patient is a woman of 67, who was first admitted eight years ago complaining of chronic cough and shortness of breath for many years. She suddenly noticed fever, marked increase in dyspnea and cough, and was admitted to the hospital. X-ray showed a bronchopneumonia. She was extremely ill for about three weeks, requiring continuous oxygen therapy, and although the prognosis was grave when she was admitted, she was discharged much improved and made an uneventful convalescence. At the time of discharge the diagnosis was chronic bronchitis and emphysema; marked interstitial fibrosis; minimal, apparently healed apical pulmonary tuberculosis, more pronounced on the left than on the right side; and a recent acute suppurative bronchopneumonia.

During the subsequent years she felt relatively well. She continued to have a mild, productive cough and dyspnea, but these symptoms did not increase. During one of her follow-up visits about two years ago it was observed that she was hoarse. Laryngoscopy disclosed a right recurrent laryngeal nerve paralysis. The significance of this was not clear, since she did not show any new developments on physical or x-ray examination. Bronchoscopy revealed no evidence of bronchial disease. What we were looking for at that time was the presence of a neoplasm. The patient continued under observation first at short and then at longer intervals with no new developments.

About three or four months ago, her private physician, during a routine fluoroscopy, observed a new lesion in the left infraclavicular area at the site of a previously observed calcified tuberculous focus. He thought this was a reinfection type of tuberculosis, despite the fact that the patient was 67, and continued observation showed that the shadow was enlarging.

About the same time she began to lose weight, and noticed pain in the left shoulder region and the upper part of the back. These symptoms, in combination with progression of the x-ray shadow led to her admission to the hospital for further study.

*X-ray examination* of the chest on admission showed interstitial fibrosis in both lungs and the small areas of calcific tuberculosis in both apical fields which had been noted eight years earlier (fig. 1). In addition, in the left clavicular area, the calcified tuberculous focus was surrounded by a large homogeneous density.

The lesion represented by this newer shadow did not produce any abnormal physical signs, and although the patient had a great deal of pain, only a slight amount of localized tenderness was elicited in this region posteriorly.

The differential diagnosis rested between tuberculosis and neoplasm. In order to reach a final diagnosis, with the lesion situated posteriorly close to the chest wall, three diagnostic aspirations were performed. The result of the first biopsy was inconclusive. The second and third biopsies were reported as showing a number of cells suggestive of carcinoma.

The shadow continued to enlarge. Repeated examination of the sputum and of the stomach washings for tubercle bacilli were negative, and the diagnosis of carcinoma seemed justified at this time.

*Comment.* The interest in this case lies in the fact that this was a patient who had old tuberculosis and who developed a lesion in the left infraclavicular region which was strongly suspicious of reinfection tuberculosis. Ordinarily the case

\* Presented as part of the Thoracic Disease Conference at The Mount Sinai Hospital, New York, November 6, 1944.



FIG. 1. Diffuse fibrosis in both lungs with small areas of calcific tuberculosis in both apices. Large homogeneous density in left upper lobe.



FIG. 2. Scattered nodular densities throughout both lung fields with a homogeneous large density in the left upper lobe.

would be diagnosed as tuberculosis, and this diagnosis was originally made. However, because of the manner in which the shadow enlarged, and particularly because of the associated pain in the back, the presence of carcinoma was suspected and was more or less proven at the time by the strongly suggestive biopsy findings. This diagnosis has recently been confirmed at postmortem examination.

This patient's grandchildren were exposed to whatever disease she had and the family was anxious to establish or exclude the diagnosis of open, progressive tuberculosis. Further, the prognosis is quite different in the case of carcinoma of the lung than it is in tuberculosis.

Another point of interest was the right recurrent laryngeal paralysis, which antedated this new lesion by at least two years. The significance of this is not clear even now.

The possibilities are, first, that it had no relationship at all to the neoplasm on the left side. Some, however, suggested the possibility of a neoplasm, perhaps a small one, on the right, from which a blood-borne metastasis developed on the left. The involvement of glands on the right side might be responsible for the paralysis of the right recurrent laryngeal nerve. Against this supposition is the negative bronchoscopy two years ago, and a comparison of the old and new films, showing no significant change on the right side. One would expect that after two years there would be something on the right side to suggest the primary focus there.

*Case 2.* This patient a woman aged 84, about a year and a half ago was investigated for tuberculosis. This was occasioned by the discovery of tuberculosis in a grandchild. A lesion was found, but at that time it was apparently inactive, and confined to both upper lobes.

The patient remained under observation. One year later, a fresh lesion was found in the left infraclavicular area and active tuberculosis was suspected; but repeated sputum examinations and temperature records did not confirm this diagnosis. At the same time the patient began to lose weight which was difficult to explain in the absence of fever and other constitutional symptoms.

Another feature was noted on x-ray examination. In addition to the large density in the left infraclavicular region there were many smaller densities scattered throughout both lung fields (fig. 2). These became larger and more obvious a few months later.

*Comment.* Here, again, the practical problem was to determine whether this represented a reinfection type of tuberculosis and, if so, whether it was a progressive lesion. The question of contact with grandchildren was also of great importance. The subsequent clinical course, the manner in which the densities enlarged, and the fact that other metastatic lesions developed prove the diagnosis of carcinoma.

It is still undecided whether the primary lesion is in the lung or whether the pulmonary foci represent hematogenous metastases from another source. So far no other focus was discovered and it is assumed that the patient has a primary carcinoma of the lung.

## ANTERIOR MEDIASTINAL NEOPLASM WITH UNUSUAL X-RAY APPEARANCE\*

C. B. RABIN, M.D.

These two cases represent tumors in the anterior mediastinum. I am not sure whether the first tumor is a neoplasm or not. It offers a problem for differential diagnosis.

*Case 1. History.* The patient, a man of 30 years, at the time of his induction into the Army two or three months previously, revealed a density on x-ray examination. The lesion gave rise to no symptoms or abnormal physical signs. The x-ray film shows a circular shadow in the right cardiophrenic angle, and on the lateral view it is seen situated adjacent to the anterior chest wall (figs. 1 and 2).

*Comment.* Shadows such as shown in this case may be caused by various lesions. The first to be considered was a hernia through the foramen of Morgagni. The stomach and colon were therefore x-rayed to see if there was any air-containing viscus in this region with negative results.

A diagnostic pneumothorax was then done to see if the mass could be separated from the lung and to determine whether the lesion arose from somewhere in the mediastinum. A film was made with the patient in the Trendelenburg position. The pneumothorax was not very large and the mass could not be separated from the lung.

The lateral view, however, made in the Trendelenburg position, showed the mass to be sharply demarcated, oval in shape, and its lower border seemed to be separated from the diaphragm. Offhand, this would seem to indicate the absence of any connection between the mass and the subphrenic region. Such a connection is not excluded by this finding, however, although it makes it less likely.

One of the lesions that will cause a shadow such as this in the cardiophrenic angle is a herniation of pro-peritoneal fat through the foramen of Morgagni. The fat enters the mediastinum and then juts out into the right pleural cavity.

In such an instance, one might conceivably get a film just like this in the lateral view, with the lower border of the mass separated from the right leaf of the diaphragm. There would not be any separation in the midline, but this connection would not be visible on the film. However, the absence of a visible connection with the diaphragm does make it more probable that there is no connection between the abdominal cavity and this neoplasm.

The most likely possibility would appear to me to be a projection into the pleural cavity of a tumor that originates from the pro-pericardial fat. The possibility of a teratomatous dermoid tumor in the mediastinum cannot be excluded from this examination, but these neoplasms are usually situated higher up.

The patient is returning for exploratory operation and removal of the mass.

\* Presented as part of the Thoracic Disease Conference at The Mount Sinai Hospital, New York, November 6, 1944.

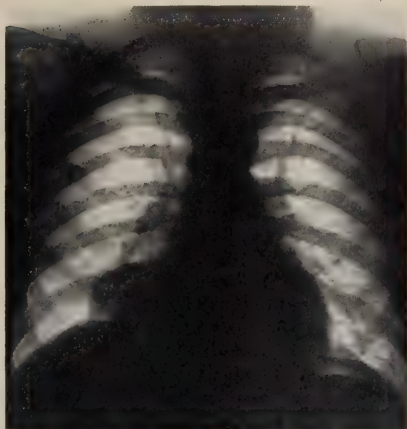


FIG. 1. Circular shadow in the right cardiophrenic angle



FIG. 2. Right lateral view showing density situated adjacent to anterior chest wall



This is not a hazardous procedure and should be done because of the uncertainty as to the nature of the tumor.

*Case 2. History.* In the second case the diagnosis could be established with fair certainty. The patient was a man, aged 35 years, who a year ago began to complain of a persistent dry cough. At the end of six months he was fluoroscoped and a mass was found in the mediastinum. He lost about ten pounds in weight before the time of his admission but did not look particularly ill. For a few months he had had slight pain in the anterior chest.

*Examination.* Some dullness was noted over the left anterior chest. The roentgen film showed an unusual lobulated shadow with a rather straight longitudinal outer border situated to the left of the mediastinum (fig. 3). The shape suggested a tumor of the thymus.

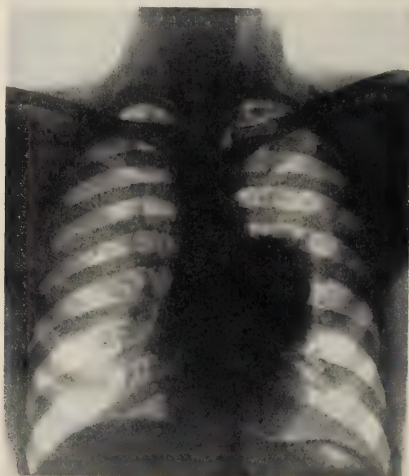


FIG. 3. Lobulated shadow with straight lateral border in region of left lung root

The position of the mass was a little low, but this is not an unusual position for a thymic neoplasm. On the lateral view, the lesion was seen to be situated anteriorly. The upper border was well outlined but the lower border was indistinct.

The blood Wassermann reaction gave first a plus-minus result, then 2+, and later a 4+ reaction, and it was felt that aneurysm of the aorta had to be ruled out. Although the location (anteriorly on the left side) would be most unusual for such a lesion, we know from sad experience that an aortic aneurysm *can* occur in this location.

Angiocardiography, therefore, was performed and the mass was seen to be situated outside the heart and separate from the aorta.

For further information and better outlining of the growth, air was injected into the mediastinum. The tumor was sharply outlined by the air along its mesial lower border, and the lower border could not be seen on the lateral view. In the left oblique position, the bizarre shape of the mass with its straight outer border, suggested a tumor of the thymus.

Because previous blood Wassermann tests had apparently been negative when he gave blood for transfusion a year and again six months previously, and because the Kahn and various other tests were negative, it was concluded that he did not have syphilis. It was decided to explore the mass with a view to removing it. Although we felt that there was a fair chance that the tumor was malignant, we believed that it might be removable even if this proved to be the case.

An Aschheim-Zondek test, done before the operation, was negative.

*Course.* At operation, a lobulated growth was found attached by a stalk which seemed to be related to the thymus gland. The neoplasm was resected and a piece of the stalk was removed.

On histological examination the tumor was seen to be composed of two elements: (1) cells which are larger, with pale nuclei, having an appearance suggestive of epithelial cells, and (2) numerous lymphocytes interspersed throughout the growth. This was the general picture of the growth everywhere. The nuclei varied in their staining qualities, the appearance being that of a malignant tumor. Sections were made of the stalk attached to the growth, and these revealed normal thymus tissue.

*Comment.* The combination of epithelial cells and lymphocytes throughout the tumor corresponds to a tumor of the thymus gland, and the atypical character of the nuclei would make this tumor a malignant one. Even though no Hassall's corpuscles were demonstrated, one has a right, in this case, to speak of a true thymoma. In spite of its malignant character, the neoplasm was encapsulated well enough so it could be removed. Whether the patient will be cured or will develop metastases, only the future can tell.

# CYLINDROMA OF BRONCHUS. PNEUMONECTOMY. PERIPHERAL CARCINOMA OF LUNG. LOBECTOMY AND CHEST WALL RESECTION\*

H. NEUHOF, M.D.

*Case 1. History.* This patient was first seen in 1942. She was then 42 years old and gave a history of a slight productive cough and a number of episodes of hemoptysis during the preceding year. She noticed no progression of symptoms, the cough remaining essentially unproductive and she felt otherwise quite well.

At the time of her admission in 1942 she was bronchoscoped and a specimen was removed from the anterior wall of the right main bronchus, which was found to be hard. The mass extended to the orifice of the right upper lobe bronchus.

Microscopic examination of biopsied material revealed cylindroma, which is essentially a non-malignant neoplasm with, however, some tendency towards local spread and what might be termed "local malignancy." The evidence is that this is a lesion which either does not metastasize or does so very slowly.

Apparently nothing happened between 1942 and her recent admission to the hospital in 1944, that is, in so far as the roentgen evidence was concerned.

In the posterior-anterior film there is visible a circumscribed shadow, partly a neoplasm and partly an atelectasis of the middle lobe (fig. 1). Its outline also is seen in the lateral film (fig. 2).

*Course.* When this patient was operated upon, a mass was found in the region of the hilum. As far as circumscription was concerned, one can describe this lesion as a mass which was circumscribed superficially within the lung but invaded diffusely the tissues of the mediastinum for an indeterminate distance alongside and around the main bronchus.

*Comment.* The extent of the invasion by this tumor (which is classified as a benign tumor), is realized when I state that pneumonectomy was carried out in this case without the ligation of a single vessel. At the hilum, the tumor was cut across because the tumor could not be removed on account of the extension into the mediastinum for an indeterminate distance.

Without entering here into a discussion of the technical aspects of the case, it was necessary to face the problem which existed after operation in a patient whose bronchus could not be shut off. It is obvious that the patient has not been cured. It is still uncertain as to what will happen to what is left of the cylindroma. Then again, we have a patient with a patent bronchial stump and a large dead space in the right chest for which a series of thorocoplastic procedures were required.

This, then, is a so-called benign or non-malignant tumor which has developed locally invasive characteristics.

*Case 2.* By way of contrast, we have the other patient who is sixty years old and whose history was of two months' duration with pain in the left chest without any additional features other than some anorexia and a loss of some fifteen pounds in weight.

During this patient's two weeks' stay in the hospital, he ran fever between 99 and 101. The essential features are to be seen in the x-ray films. There is a well-circumscribed

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\*Presented as part of the Thoracic Disease Conference at The Mount Sinai Hospital, New York, November 6, 1944.

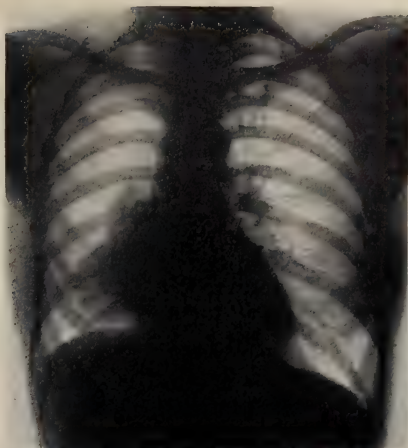


FIG. 1. Circumscribed mass in region of right middle lobe



FIG. 2. Right lateral view showing anterior location of mass in the region of the middle lobe with atelectasis of this lobe.

shadow as far as its mesial aspect is concerned which spreads outwards into the thoracic wall (fig. 3). In an over-exposed film there is to be seen some separation of the fourth and fifth ribs with thinning of the ribs where they face each other. This appearance could be due either to bone absorption as a result of pressure, absorption from any tumor, or by direct invasion of rib by a malignant tumor.

The reason for the febrile course was explained at operation by the finding of suppuration. There was but little question as to the diagnosis here. The markedly circumscribed feature of the lesion was well seen at operation. It was not necessary to remove more than the lower lobe, the adjacent portion of the upper lobe (because of the situation of the tumor), and the thoracic cage where it was invaded as revealed by the x-ray film. The excised specimen of the lesion in the lung disclosed an abscess in addition to carcinoma.

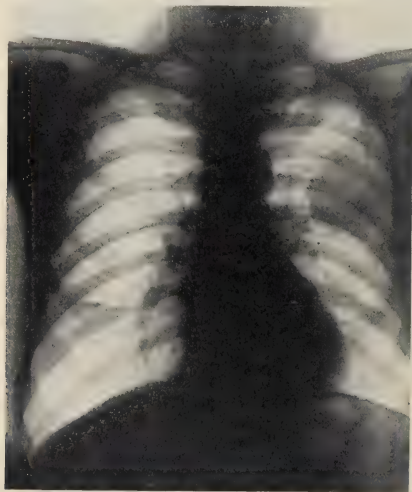


FIG. 3. Circumscribed density situated at the level of the fifth to seventh ribs on the left

*Comment.* In this case there were no regional nodes involved. It is characteristic of circumscribed cancer of the lung to have no involved regional lymph node by way of contrast with many of the main bronchus cancers in which regional lymph node involvement is apt to be early and extensive. It is for this reason that we, in this clinic, feel that in cases of circumscribed cancer of the lung not infrequently operations less extensive than pneumonectomy may achieve lasting results. Indeed, the sole factor which may vitiate the result in such cases may be the existence of remote blood-borne metastases (brain, etc.) already existent at the time of operation but not recognizable on physical examination.



# ESSAYS ON THE BIOLOGY OF DISEASE<sup>1</sup>

ELI MOSCHCOWITZ, M.D.

## CHAPTER 11

### ARTERIOSCLEROSIS

The term "arteriosclerosis" has at present a stricter connotation than formerly employed. It does not comprise all lesions of vessels that cause thickening of the walls; for instance: luetic arteritis, periarteritis nodosa, the lesions accompanying rheumatic fever, lupus erythematosus, subacute bacterial endocarditis, thrombo-arteritis obliterans and thrombo-angiitis obliterans. There is ample testimony that the medial calcification of Mönckeberg is a different disorder, although both are often associated. Arteriosclerosis however cannot be defined by a process of exclusion. A precise definition, as we shall see, is difficult for a number of reasons. First, because it is a summation of many processes, one or more of which may be absent; second, because arteriosclerosis represents a wide biological range, so that the variety, extent and intensity of the lesions vary with the senescence of the process; and third, because the development of the lesions is modified by the structure of the artery and its topographical peculiarity. Despite this complexity, there are certain common factors. 1) it is a progressive process beginning already at an early age; 2) it is irreversible; 3) hyperplasia of one or more coats is exhibited; 4) some degree of thickening is always present; 5) dilatation, elongation and deformity are present; 6) there is a loss in elasticity.

We therefore suggest the following definition: *Arteriosclerosis is a progressive and irreversible affection in which hyperplasia of one or more coats is a primary reaction, with deposition of collagenous, lipoid, hyaline and calcium as a secondary reaction, the totality of both components resulting in thickening, dilatation, deformity and loss of elasticity of the walls.* This definition applies particularly to the advanced lesions observable in the senescent years, but what constitutes the earliest stages of arteriosclerosis is still a matter of keen debate. The answer cannot be given without a study of the morphology and growth of vessels from intrauterine life to advanced years. Under such conditions it will become apparent that normal physiological growth merges so imperceptibly into morbid changes that it is impossible to determine where one ends and the other begins.

Regrettably, most studies on arteriosclerosis have been limited to the lesions of the larger arterial trunks. As I have pointed out previously, (1), the study of morphologically comparable lesions in the veins, the capillaries, the arterioles

<sup>1</sup> This is the eleventh chapter in a series of essays by Dr. Eli Moschcowitz, in which an attempt will be made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. When the publication of the projected series of essays is completed, the several installments will be assembled and printed as a monograph.—Ed.

and even within the chambers of the heart, throws light upon the genesis and significance of the component lesions comprised under the term "arteriosclerosis."

The earliest vessel in the human embryo is a simple tube of mesenchyme lined by endothelium. During the fourth month of intrauterine life, the arteries acquire their three main layers: the intima, media and adventitia, (2, 3, 4), and the different tissue elements of which the wall of the vessel is composed: the elastica, the smooth muscle and the connective tissue, are already differentiated. Henceforth, the structural development proceeds somewhat differently depending on whether the vessel is of the elastic type such as the aorta, or of the muscular type such as the brachial artery.<sup>2</sup> In the aorta during the fourth month, the intima consists only of endothelium lying directly on the thick internal elastic layer. The media consists of several layers of muscle fibres, interlaced with an abundance of anastomosing elastic fibres. The adventitia, a layer of embryonic connective tissue, is thicker than the media. At the end of embryonal life, a thin connective tissue layer in the intima becomes visible, while the internal elastic layer thickens and begins to split. The elastic network within the media increases greatly. The muscle elements also increase, but not proportionately to the elastic elements. The adventitia becomes narrowed.

In the muscular arteries, in the fourth month of intrauterine life, the intima again consists only of an internal elastic layer directly covered by endothelium. The comparatively thinner muscular media contains relatively few elastic fibres. Between the media and the adventitia a well circumscribed elastic layer is developed, the elastica externa. The adventitia consists of two layers, an outer of connective tissue and an inner containing elastic elements. This elastic layer is entirely missing in the aorta. At birth, the internal elastic layer becomes thicker. The medial circular muscular coat increases in width, and contains, as compared to the aorta, but few and thin elastic fibres which continue into the internal and external elastic layers. The inner elastic layer of the adventitia is greatly increased.

In post-uterine life, the vascular system, in contradistinction to most of other organs of the body, continues in the process of differentiation, and it is in the interpretation of these changes that difficulty arises as to when the physiological becomes pathological.

In the arteries of the elastic type, the inner elastic later shows a progressive splitting into two or three layers; on its inner aspect a musculoelastic layer appears, the components running longitudinally. Farther toward the lumen there is formed a thin layer of collagenous fibrous tissue containing delicate elastic fibres on which rests the endothelium. Most observers follow the nomenclature of Jores (5), who terms the split layer of the elastica intima the "hyperplastic intimal layer", and the collagenous fibrous elastic layer as "the regenerative connective tissue layer." These layers of the intima continue to increase in thickness, and are not fully differentiated until the 30th year.

<sup>2</sup> There is no hard and fast distinction between these two types. They merge into each other as one proceeds from the periphery to the aorta.

In arteries of the muscular type similar changes occur, except that the muscular components overshadow the elastic in growth. The elastica in the media grows but does not form distinct lamellae. In the intima a hyperplastic elastic layer of thin dimension develops, but a musculo-elastic layer does not arise except near the areas of exits of branching vessels. A connective tissue layer forms between the endothelium and the inner elastic layer of the intima.

Although the structural changes proceeding from intrauterine life to adulthood are somewhat different in these two kinds of arteries, the change is essentially one of degree rather than of kind, and for our purpose these differences are unimportant. It suffices to appreciate that there is a steady growth of both elastic and collagenous elements that proceeds uninterruptedly into maturity. Thus Foster (6) finds a progressive increase in elastic fibres up to the 35th year. A quiescent period then occurs for about 10 to 15 years, when degenerative changes, lipoid and calcareous, set in. The wavy contour of the elastic fibres is almost lost and the fibres stain differently with Sudan III, being converted into elascin (Unna). He did not find an actual loss of elastic tissue. That active growth of connective tissue is progressive in vessels of maturer years is a well attested observation, not only in the intima but in all the coats, including the adventitia.

In the light of the investigations of Winternitz and his co-workers (7), who found an extensive network of vasa vasorum in the walls of both normal and diseased vessels, arising both from the adventitia and the intima, it intrigues us to think that part at least of the formation of new collagenous tissue may be the result of blockage of these vessels, comparable to the process that takes place in the myocardium in coronary disease. In part, the increase with age is the result of lipoid deposits. An untoward growth of such connective tissue in respect to the age of the individual is regarded by some as the beginning of arteriosclerosis, but inasmuch as the amount of such growth possesses such a wide range in adult life, this differentiation is hardly justified, except in instances of juvenile arteriosclerosis.

These hyperplastic intimal changes have been viewed by some as the result of "wear and tear", an indifferent term that covers so wide a range of influences that it represents only a blanket indictment. More particularly, Aschoff (8) describes these changes as an adaptation to the increasing intravascular pressure that proceeds from birth to adulthood. This view we regard as amply justified on a number of grounds. 1. Under the influence of increased intravascular pressure within the greater circulation these hyperplastic changes are intensified. This is particularly striking in cases of so called malignant hypertension; 2. The independence in incidence, as I have pointed out (1), between gross arteriosclerosis of the pulmonary vessels and those of the greater circulation. Gross arteriosclerosis of the pulmonary circulation is practically never observed except in instances where an increased pressure within the pulmonary circuit can be predicated; in mitral stenosis, for example. The reason for the comparative absence of gross arteriosclerosis in the pulmonary circuit even in middle aged adults is due to the fact that the intravascular

pulmonary pressure is only one-sixth that in the aorta [Starling (9)]; 3. A marked retinopathy, which is recognized (10) as an arteriosclerotic process, is practically absent unless a considerable degree of hypertension of the greater circulation is present; 4. Phlebosclerosis, a lesion morphologically comparable to that of arteriosclerosis, arises only when a local or a general increase in intravenous pressure is present. This is nicely illustrated in phlebosclerosis of the hepatic veins (11), in the portal circulation (12), and in the venous segment of an arterio-venous aneurism (13). The remarkable freedom, under normal circumstances, of hyperplastic changes in the veins is readily understandable in view of the extremely low pressures that exist within the venous system.

Obviously, the time factor must be taken into consideration, even under conditions of intravascular pressures within the range of normal. In this connection it is interesting to note that in rats and mice such intimal hyperplastic changes are not found, while in comparatively long-lived animals such as horses and cows they are well marked; whereas in cats and dogs, whose life range falls in between these extremes, the changes are comparatively slight (14).

Fox (14) states that there is a distinct difference between the appearance of arteriosclerosis in the shorter-lived mammals and in longer-lived animals, such as birds; he also points out that animals which revealed arteriosclerosis at autopsy had been in captivity nearly twice as long as the average exhibition period for their order and family. As further evidence we may cite the fact that gross arteriosclerosis may be seen in the pulmonary artery of an individual of advanced age (usually past 70) even without an associated hypertension of the pulmonary circuit (15). Therefore, when hypertension enters, the normal hyperplastic intimal changes occur earlier, and are intensified. This accounts in every instance for juvenile arteriosclerosis in the greater circulation, and also in the lesser circulation, where it has been observed even in the first years of life in association with congenital cardiac defects (16, 17).

The crucial problem now arises as to when physiological aging ends and arteriosclerosis begins. While some observers recognize the difficulty of such a differentiation, (2, 19, 20) the vast majority, headed by Jores (21), hold that arteriosclerosis begins only when various forms of "degeneration" set in, especially fatty and, to a lesser degree, mucoid, calcareous, and hyaline. No difficulty in interpretation arises when these degenerative changes present themselves in a pronounced form, such as in gross arterioma, in extensive calcific deposits or marked hyalinization. Unfortunately, Jores and his followers have not taken into consideration the fact that these substances are already normally present at an early age, some of them even at birth, and the problem arises whether these profound expressions represent no more than exaggerations of normal trends, comparable to the physiological aging represented in the hyperplasia of the intima and elastica. Furthermore, these observers have failed to appreciate that hyperplastic changes alone may give rise to a morphological picture consistent with arteriosclerosis even in the absence of any "degenerative" changes whatever. This is notably evident in arteriosclerosis. We shall discuss these "degenerative" changes in order.

a. Lipoid deposits are exceedingly common in children in the intima of the aorta, just above the cusps, and unassociated with any productive change. From the fourth year on these lipoid deposits are almost constant. In the second decade, they are distributed throughout the aorta, especially at the sites of stresses, for instance on the proximal side of the exits of the coronary and intercostal vessels [Zinserling (22)]. From the third decade onward, these lipoid deposits are deposited at other sites of the aorta, often haphazardly, but sometimes particularly prominent at the sites of the intervertebral discs (Westenhoffer) (23). Confluence of these lipoid areas leads to atheromata which penetrate more deeply into the vascular coats. There is excellent evidence that these lipoid deposits stimulate the growth of collagenous tissue, (24, 25, 26), accounting for part of the growth of this tissue in the advancing years. These lipoid areas resemble precisely, both in conformation and distribution, those produced by Anitchkow (24) in his feeding experiments; whether they ever regress in the human being is entirely conjectural.

There has been much debate as to whether these early fat deposits represent the true beginnings of arteriosclerosis. Jores and others believe they do not, and that one can speak of a genuine arteriosclerosis only when these deposits are associated with an intimal hyperplasia. Curiously, of all the varieties of "degenerations", why Jores should choose the lipoid as the essential characteristic of arteriosclerosis is difficult to discern. Inasmuch as he admits that such intimal hyperplasia is already evident in the earliest years of growth, we fail to see the validity of his definition unless we accept the fact that arteriosclerosis begins at birth, which he does not admit. On the other hand, it is highly questionable whether lipoid, either in the form of small plaques or atheromata, is a facultative or a necessary component of arteriosclerosis. In arteriosclerosis, characterized by enormous thickening due to intimal hyperplasia, both of the collagenous and elastic components, together with hyalinization, lipoid changes do not occur except in the later stages (26). Even in larger vessels, sclerotic patches in the intima may occur without lipoid (27). It is imperative to emphasize, therefore, that a distinction should be made between the terms arteriosclerosis and atherosclerosis, terms unfortunately too often employed interchangeably.

b. Mucoid "degeneration" of arterial walls has also been regarded as a component of the arteriosclerotic lesion (28), but there is abundant and strong evidence, particularly demonstrable by chromotropy (Kresylviolet method) that it is already present in the embryo. In post-embryonic life it increases in quantity proportionately to the increase in both the elastic and connective tissue structure, and in adult life it is present in the media between the muscle cells and the elastic fibres (29, 30). In the smallest vessels chromotropy disappears. In this respect also, as in lipoid changes, one cannot distinguish between the physiological and the pathological.

c. Calcareous "degeneration", especially in massive form, is conventionally held as indicative of arteriosclerosis. However, calcium can be demonstrated in the intima and media, especially by the silver nitrate method even in the



earliest years of life (31). Jores (21) finds it even in the first year, especially in the vessels of the pelvis, and in the early years of life in the common iliac artery. After the tenth year it is found uniformly in the abdominal vessels and in the aorta. After the 20th year it is found in all the larger vessels (32). As Faber (33) has shown, these early fine deposits of lime are unassociated with any degenerative tissue changes, especially lipid. What relation these early deposits have to the pronounced calcific deposits seen in elderly life, or to the process termed "medial calcification" of Mönckeberg [a process comparable to that produced experimentally by ergosterol (34) or adrenaline (35)] is speculative. In the study of vessels in the later periods of life, Klotz (36) finds that the calcification is a secondary process and bears a distinct relation to the lipid content of the tissues. There is also no doubt that hyalinization predisposes to calcification. The tendency for calcium to deposit in dead or inert tissues and later to be transmuted to bone is well known (37, 38). Nevertheless, it is questionable whether calcification is an inevitable accompaniment of arteriosclerosis, unless again we assume that the earliest hyperplastic changes already represent the beginnings of the process.

d. Hyaline change is exceptional in the earlier years, although it is found in the arterioles of the spleen as early as the tenth year (39). In the sense that hyaline normally is not found at birth, it may be termed a "degeneration", although its significance in the body economy is not clear. Hyaline is a common lesion in aging arteries, especially in the arterioles (40), and is particularly prominent in hypertensives. It is also seen in the walls of capillaries that have been subjected to increased intracapillary pressure (41, 42). Nevertheless, hyaline is not necessarily a part of the arteriosclerotic process, but a facultative one, similar to the lipid, mucoid and calcareous changes.

The hyperplastic intimal changes that we have outlined as occurring in the larger vessels are precisely duplicated in the smaller branches: in the kidneys (43), in the spleen (44), in the coronary vessels (45, 46, 47), in the brain (48), in the radial (49) and pulmonary arteries (50). Under conditions of increased intravascular pressure they come earlier and are intensified. The same processes occur in animals that reach an age comparable to that of man.

From this discussion, it is apparent that the dividing line between physiological aging and the lesions conventionally grouped under the term "arteriosclerosis" is indefinite and that one merges into the other. One cannot conceive of arteriosclerosis as an inflammatory process, as Virchow insisted, or as a metabolic disorder (except perhaps in respect to the lipid component), but rather as a normal compensatory process or adaptation to various factors, of which the progressive increase in intravascular pressure is by far the dominant one. It is only in this sense that we may speak of "wear and tear." The term "hyperplastic" arteriosclerosis applied by Evans (51) is superfluous.

The term "primary" arteriosclerosis has often been employed, with the implication that there is a "secondary" type. Curiously enough, the term "primary" has been confined entirely to those forms of arteriosclerosis of the pulmonary artery for which no cause is found, such as hypertension of the

pulmonary circuit. I have discussed this matter previously (1). On analysis of the very few reported cases, I question whether a "primary" arteriosclerosis of the pulmonary artery exists. In the sense that arteriosclerosis represents a compensatory adaptation, the terms "primary" or "secondary" have little significance. This applies particularly to "Ayerza's disease", a malady without the slightest nosological status.

In other words, arteriosclerosis is a process which begins at birth (and perhaps before) and is an inevitable destiny of mankind. The process may be influenced by other factors, for instance, intravascular pressures, feeding, perivascular stresses and fixations (1), congenital or acquired abnormalities, and undoubtedly other as yet unknown factors, but it never can be completely escaped. This obviously does not imply that clinical and anatomical arteriosclerosis are equivalent. Arteriosclerosis causes disease only when the circulation of a vital organ is seriously compromised or when the weakened wall ruptures.

# BIBLIOGRAPHY

1. MOSCHCOWITZ: Vascular Sclerosis. New York, Oxford Press, 1942.
2. MAXIMOW AND BLOOM: Histology, ed. 2, Philadelphia, W. B. Saunders, 1934.
3. ASCHOFF, A.: Über Entwicklungs—Wachstums, und Altersvorgänge an dem Gefässen von Elstischen und Muscularen Typus. Jena, 1909.
4. BENNINGHOF: Hand. der micros. Anat. des Menschen. Berlin, 1920.
5. JORES: Handb. der spec. path. Anat. u. Histologie (Hencke-Lubarsch). Berlin, 1924, Bd. 11, p. 608.
6. FOSTER: J. Med. Research, 21: 297, 1909.
7. WINTERNITZ, THOMAS AND LE COMPTE: The Biology of Arteriosclerosis, Springfield, Ill., C. C. Thomas, 1938.
8. ASCHOFF, L.: in Arteriosclerosis, edited by E. V. Cowdry, New York, Macmillan & Co., 1933.
9. STARLING: Human Physiology. Philadelphia, Lea & Febiger, 1915.
10. COLLINS AND MAYOU: Pathology and Bacteriology of the Eye, P. Blakiston's Son & Co., 1925.
11. MOSCHCOWITZ: Emanuel Libman Anniversary volumes, International Press, 1932.
12. SIMMONDS: Virchows Arch. f. path. Anat., 207: 360, 1912.
13. BENDA: Hand. s. spez. path. Anat. u. Hist., Hencke-Lubarsch, Berlin, 2: 787, 1924.
14. FOX: in Arteriosclerosis, edited by E. V. Cowdry, Macmillan & Co., New York, 1933.
15. LJUNGBERG: Arteriosklerose des kleinen Kreislaufs, Wiesbaden, J. F. Bergman, 1915.
16. ZUR LINDEN: Virchows Arch. f. path. Anat., 252: 220, 1924.
17. WATJEN: Zeit. f. allg. Path. u. path. Anat., 38: 544, 1926.
18. MÖNCKEBERG: Klin. Woch., 3: 1473, 1521, 1924.
19. ASCHOFF, A.: Über Entwicklungs—Wachstum und Altersvorgänge in dem Gefässen von Elastischen und Muscularen Typus. Jena, 1909.
20. FISHER, WASSELS AND JAFFE: Hand. d. normalen u. pathologischen Histologie, Berlin, 7: 2, 1927.
21. JORES: Hand. der spez. path. Anat. u. Hist. (Hencke-Lubarsch), Berlin, 1924.
22. ZINSERLING: Virchow's Arch., 255: 677, 1925.
23. WESTENHÖFFER: Med. Klin., 20: 643, 1924.
24. ANITCHKOW: in Arteriosclerosis, edited by E. V. Cowdry, New York, Macmillan & Co. 1933.
25. FISHER: Hypertension and nephritis., ed 4, Philadelphia, Lea & Febiger, 1939.
26. BEITZKE: Virchows Arch., 267: 625, 1928.
27. HUECK: München. med. Wehnschr., 67: 535, 573, 606, 1920.

28. BJÖRLING: Virchows Arch., 205: 71, 1911.
29. SCHULTZ: Virchows Arch., 239: 415, 1922.
30. POLICARD: in Arteriosclerosis, edited by E. V. Cowdry, New York, Macmillan & Co., 1933.
31. MÖNCKEBERG: Virchows Arch., 171: 141, 1903.
32. FABER: Die Arteriosklerose. Jena, 1912.
33. WENZEL: Arch. f. Spec. Path. u. Pharmacol., 137: 215, 1930.
34. JOSUÉ: Press Med., 11: 798, 1903.
35. KLOTZ: J. Med. Research, 27: 27, 1915.
36. MOSCHCOWITZ: Bull. Johns Hopkins Hosp., 27: 71, 1916.
37. WELLS: Arch. Int. Med., 7: 721, 1911.
38. HERXHEIMER: Berlin, Klin. Woch., 1917.
39. MORITZ AND OLDT: Am. J. Path., 13: 679, 1937.
40. MOSCHCOWITZ: Am. Heart J., 6: 171, 1930.
41. PARKER AND WEISS: Am. J. Path., 21: 57, 1918.
42. OPPENHEIM: Frankf. Zeit. f. Path., 12: 573, 1936.
43. NAKONETSCHNY: Virchows Arch., 145: 564, 1924.
44. WOLKOFF: Virchows Arch., 141: 42, 1923.
45. GROSS, EPSTEIN AND KUGEL: Am. J. Path., 10: 253, 1934.
46. EHRLICH, DE LA CHAPELLE AND COHN: Am. J. Anat., 248: 241, 1931.
47. HACKEL: Virchows Arch., 266: 630, 1927.
48. HALLENBERGER, DEUTSCH: Arch. f. Klin. Med., 87: 62, 1906.
49. TORHORST: Beitr. z. path. Anat. u. allg. Path., 36: 210, 1904.
50. EVANS: Quart. J. Med., 14: 215, 1921.

## Herman Schwarz

October 24, 1876—May 19, 1945

Dr. Herman Schwarz, a graduate of the College of the City of New York, received his doctor's degree from the College of Physicians and Surgeons of Columbia University in 1898, and on entering the Mount Sinai Hospital as an interne began his 47 years of loyal service to this institution.

Dr. Schwarz was one of the first physicians in this country to devote himself entirely to the practice of the medical care of children. Even while serving his internship, Dr. Schwarz became interested in pediatrics, and soon afterward went to Germany to study with the pioneer pediatricians Baginski and Heubner. Upon his return he became associated with Dr. Henry Koplik, and in 1904 he was appointed chief of the pediatric out-patient department. Three years later he became Adjunct Pediatrician, in 1922 Associate Pediatrician, and in 1945 Consultant Pediatrician of the Mount Sinai Hospital. He also served as Attending Pediatrician of the Beth Israel Hospital for 14 years from the time of his appointment in 1930.

Dr. Schwarz realized early in his career that facilities for well-baby care among the less privileged were inadequate throughout the city. To meet such a need, he, in association with Dr. I. L. Hill, an obstetrician, established a clinic, the forerunner of the Baby Health Stations in New York. It had a most modest beginning, occupying the ground floor of a tenement house. The babies were delivered in their homes, where they received postnatal care from visiting physicians. Subsequently, during the first year, they were then cared for at the clinic. In 1908, with the aid of a donation by John Berwind, a large modern building was constructed as the Free Outdoor Maternity Clinic. Later, and again through the generosity of the Berwinds, it was replaced by a larger building, the Berwind Maternity Clinic. Here, facilities were also provided for the care of the premature infant. It served to train many young pediatricians in infant care and feeding. Observations made at this clinic led to an important report on infant mortality in relation to both disease and social condition.

Soon after this report appeared, Dr. Schwarz was made a director of the American Association for the Study and Prevention of Infant Mortality. In 1923 Dr. Schwarz became a member of the Executive Committee of the Child Welfare Federation, and in this capacity he was instrumental in establishing a depot for the collection and distribution of human milk in New York City.

Dr. Schwarz was active on many committees, both lay and professional, and gave much of his time and effort as the Medical Director of the Josephine Home for Anemic and Undernourished Children, Chairman of the Physicians' Division of the United Jewish Appeal, member of the Medical Board of the Home for the Jewish Blind, and member of the Emergency Committee for Displaced Foreign Physicians. He was also Medical Advisor to several foundations for medical research, and was a charter member of the American Academy of Pediatrics.



Herman Schwarz



His many contributions to pediatrics included important studies on causes of infant mortality, alimentary intoxication in infancy, nephritis, and rheumatic fever.

As a self-reliant clinician, Dr. Schwarz endeavored to recognize from the bedside examination and observation of the patient the character and seriousness of the illness. Although he was always ready to avail himself of new scientific methods, he felt that a competent practitioner should learn much about his patient even before employing laboratory aids. This was what he meant when he repeatedly said that it was important to become a "good doctor."

Characteristic of Dr. Schwarz' inquiring mind was its skepticism. He never took anything for granted, frequently posing the question, "How do you know?" Whether based on time-honored medical tradition or on new theories, an explanation never satisfied him unless it was proven beyond a doubt. This philosophy inspired him in his clinical investigations and in his guidance of younger men in the field of research.

In his later years, Dr. Schwarz spent much of his time in both the clinic and the laboratory studying rheumatic fever. He was concerned mainly with the desire to alleviate the great suffering caused by this disease. This was but one of the many ways in which he displayed his love of children and his interest in their health and welfare.

Those who were close to Dr. Schwarz remember well his restless, energetic manner and his great kindness, often masked temporarily by gruffness. Many a young man owes an inestimable debt to his generosity in time and money. While he severely censured anyone who did not measure up to his own standards of personal and scientific integrity, he himself lived up to these standards and always fought for what he believed to be right.

JEROME L. KOHN, M.D.

## Isidore Friesner

July 25, 1874–September 8, 1945

Isidore Friesner received his early education in New York, the city of his birth, graduating at the age of twenty from the College of the City of New York, where he was elected to Phi Beta Kappa. Impaired health forced him to go west. There, with his health restored, he entered the Gross Medical School of the University of Colorado, receiving his Doctor's degree in 1901.

With further improvement in his health, he returned to New York, and shortly thereafter began his training in laryngology and otology. His inherent capacity for rapid acquisition of knowledge and skill was soon rewarded by appointments in well-known centers of his chosen field. His first appointment was that of adjunct surgeon, under the guidance of Dr. Wendell Phillips, at the Manhattan Eye and Ear Hospital. From then on his rise was rapid; after having joined, in 1920, the attending staff of The Mount Sinai Hospital as Associate Otologist, he became within one year chief of the Department of Otology, succeeding Dr. Fred Whiting. In the following sixteen years, as head of the department, he was responsible for developing this service as an important training center for young men, for establishing it as a nucleus for pathological research, and for making highly useful contributions in this field of investigation.

Upon retirement from active ward service in 1936 he was made Consulting Otologist. In such capacity he also served the Beth David and Bronx Hospitals in New York, and the Methodist and other hospitals in Brooklyn. He also served as consultant to the Andrew Freedman Home and the Guild for the Jewish Blind.

Among the many honors which were bestowed upon him by his colleagues, he valued, above all, two: the Presidency of the American Otological Society (1939-1940) and the Presidency of the Medical Board of The Mount Sinai Hospital (1927-1938). In the latter capacity, by virtue of his friendly personality, he was able to establish a cordial relationship between the members of the Board of Trustees and those of the Medical Board. He won the full confidence of the late president of the Hospital, Mr. George Blumenthal, and this laid the foundation for continued successful cooperation between these two bodies.

He was a member of the American Laryngological, Rhinological and Otological Society. He served as Vice President of the New York Otological Society and as Vice President, for a long term of years, of the New York League for the Hard of Hearing. His popularity among the membership of the American Otological Society was rewarded by his election to the Presidency in 1939, and to the office of Secretary and Treasurer which he held from 1940 until his death.

He was a fluent speaker, and his command of language was surpassed only by his great learning and clear vision. He was welcomed everywhere and invited repeatedly, from as far away as the west coast, to lecture and to teach in



Isidore Friesner

his field of eminence. With each trip he acquired new friends and new followers, adding much to his joy of life.

In his relations with all those who came in contact with him, he displayed friendship and great understanding. He could be easily approached by all, and for each one he had wise counsel and an expression of great warmth. It was a common experience to see this big-hearted man, at the end of the morning rounds, seated at the head of the long table in the attendings' room, receiving an almost unbroken stream of colleagues, associates and pupils, all anxious to greet him. All, and particularly "his boys", were addressed by him by their first names, and they in turn would address him as "chief." This was an expression of their feeling of admiration for his wisdom and kindness.

Dr. Friesner was also a great lover of the arts. He was an admirer of good music and attempted successfully to express himself in the art of painting.

In his home life, his all-absorbing interest was his loving and beloved companion, his wife, Laura. Their partnership was an unusually close one, each one bestowing upon the other infinite care and consideration.

And so we leave him, though we shall never forget him. His smile and his encouragement will always be with us, asking us to continue his life's work of service and devotion to humanity.

RICHARD LEWISOHN, M.D.

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY  
MEMBERS OF THE MOUNT SINAI STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*The Re-establishment of Esophago-gastric Continuity following of the Resection of Esophagus for Carcinoma of Middle Third.* J. H. Garlock. Surg. Gyn. & Obst., 78: 23, January, 1944.

The author reports a new operative procedure for cancers of the middle third of the esophagus. Formerly, operative therapy consisted of total excision of the thoracic esophagus and the formation of an upper chest esophagostomy opening and new gastrostomy below. The distance between the two was bridged by an external rubber tube. The new operation dispenses with these troublesome mechanical contrivances and substitutes a direct anastomosis over the arch of the aorta between the mobilized stomach and the stump of the esophagus. The operation is based on careful anatomical studies of the blood supply of the stomach. The first successful case is reported.

*The Subependymal Cell Plate (Matrix) and its Relationship to Brain Tumors of the Ependymal Type.* J. H. GLOBUS AND H. KUHLENBECK. J. Neuropath. & Exper. Neurol., 3: 1, January, 1944.

Nine neoplasm traceable in origin to the subependymal cell plate are presented. The cell form and organization were found to duplicate ependymal structures in varying degrees, sometimes assuming the characteristics of a well differentiated and highly specialized ependyma simulating the epithelium of the choroid plexus. Five of the neoplasms were identified as spongioblastoma ependymale, one as cellular ependymoma, one as papillary ependymoma and two as choroid papillomas. The stages of development and differentiation of neuroectodermal derivatives is reviewed to clarify the significance of embryonal and histogenic factors in the development of the brain tumors discussed. Medullary epithelium, spongioblasts and neuroblasts are held to be the only clearly recognizable embryonal cellular element from which all neuroectodermal cell forms arise, and evidence is cited for the assumption of the presence of a bipotential mother cell form. Emphasis is placed on the subependymal cell plate as an important source of immature embryonal residues from which neuroectodermal tumors are likely to develop under certain, still unknown, conditions. Such immature elements persist in the subependymal cell plate during the entire postnatal life. These cellular elements (spongioblasts, bipotential mother cells and neuroblasts) constitute the essential elements of the several types of neuroectodermal neoplasms, the morphology and biologic features of which are determined by the degree of maturity and the varying number of the several glial or neuronal cell forms present. The classification of ependymomas suggested by Kernohan and Fletcher-Kernohan is fully supported by these findings. It is pointed out that even the more differentiated neoplasms of this series must be considered as malignant.

*Osteosclerosis, Myelofibrosis and Leukemia.* J. CHURG AND M. WACHSTEIN. Am. J. M. Sc., 207: 141, February, 1944.

Among 97 cases of leukemia, 6 showed a varying degree of fibrosis of the bone marrow without osteosclerosis. Four of these cases were of the chronic myeloid type and were treated with Roentgen ray; the other 2 were diagnosed as subacute myeloid leukemia and



did not receive any Roentgen ray therapy. Fibrosis of the bone marrow (myelofibrosis), not associated with osteosclerosis, is therefore not uncommon in the leukemias. A case of osteosclerosis with leukemoid blood picture is described and interpreted as an instance of so-called non-leukemic myelosis. A review of the literature shows that osteosclerosis is often associated with non-leukemic myelosis and only very rarely with true leukemia.

*Sensitivity to Thiouracil (Report of three cases).* J. L. GABRILOVE AND M. J. KERT. J. A. M. A., 124: 504, February, 1944.

Nine patients with hyperthyroidism were treated with thiouracil and three manifested sensitivity to the drug. After treatment for ten days with one gram of thiouracil daily the first case complained of chilliness and malaise. The temperature rose to 102.4°F. and a generalized lymphadenopathy was noted. The following day a rash appeared. These signs and symptoms subsided promptly after cessation of the drug. In the second case on the ninth day of treatment the temperature rose to 105°F. and a rash appeared on the tenth day. The fever and rash subsided when the drug was stopped, and a week later were reproduced with a single dose of 0.2 gm. Patch and scratch tests with thiouracil were negative. A moderate leukopenia developed in the third case on the sixteenth day of treatment. All three cases were subsequently prepared with iodine for thyroidectomy.

*Coats' Disease.* J. LAVAL. Am. J. Ophth., 27: 2, February, 1944.

The history of a young girl with Coats' disease in one eye is given with the pathological description of the lesion following enucleation. The different types of pathological lesions are discussed separating the infiltrative and fibrotic from the vascular and hemorrhagic.

*Evaluation of Systolic Murmurs.* A. M. MASTER. U. S. Naval Bull., p. 307, February, 1944.

Apical systolic murmurs are common and it is often difficult to determine their significance. In civilian life it is usually possible to distinguish between functional and organic murmurs by a thorough examination, including fluoroscopy, x-ray, ECG, phonocardiogram and various functional tests. In the military services it is important to exclude recruits with organic murmurs since experience has shown that latent chronic valvular disease masquerading as a functional systolic murmur becomes manifest under the stress of warfare. In war time a systolic murmur should be considered serious unless proved of functional origin. In the Navy, if it is impossible to determine immediately whether the systolic murmur is organic or functional, the candidate should not be accepted for general service.

*Recovery of the Virus of Lymphocytic Choriomeningitis from the Erythrocytes of Infected Animals.* G. SHWARTZMAN. J. Immunol., 48: 111, February, 1944.

The virus of lymphocytic choriomeningitis may be found in association with the erythrocytes of mice and guinea-pigs during the experimental disease. The concentration of the virus in the erythrocytes has no relation to the amount present in the blood serum and the washings of the erythrocytes. The association is firm, apparently taking place in the stroma of the red blood cells. Strains of the virus differ from one another in the ability to attach themselves to the erythrocytes of mice and guinea-pigs. When a strain shows a decidedly greater virulence for one species than the other, there is observed a consistent infectivity of erythrocytes of the species for which the virulence of the strain is greater. The virus may be recovered only irregularly from the erythrocytes of mice and guinea-pigs when the infecting strain shows low virulence for both animal species.

*The Modern Treatment of Peptic Ulcer.* ASHER WINKELSTEIN. Bull. New York Acad. Med., 20: 2, 87, February, 1944.

In this Academy lecture on The Modern Treatment of Peptic Ulcer, the author summarizes 20 years of experience. Certain basic considerations are first enumerated. Then the more important modern ulcer therapies are reviewed. The therapy invented by the author, viz; the intragastric milk-soda drip therapy and its modification, the aluminum

gel drip, are fully presented. Basic physiologic studies, techniques and the results of 10 years' experience are given. The conclusion is that this type of therapy marks an important advance in the medical therapy of peptic ulcer. The surgical therapy is next discussed. Gastroenterostomy is deplored but subtotal gastrectomy is advocated. This is a permanent cure for gastric ulcer. To lessen postoperative recurrences in duodenal ulcer, anterior, subphrenic vagotomy added to subtotal gastrectomy, leading to achlorhydria, is highly recommended. In the prophylaxis of peptic ulcer the author recommends intensive therapy early in the disease and a wider recognition of the importance of psychic factors.

*Quantitative Shock Experiments.* B. KISCH. *Experimental Medicine & Surgery*, 2: 79, February, 1944.

The methods introduced by the author for quantitative studies on shock are described and data of experiments given. Of these methods the best is that of producing shock by intra-arterial injection of croton oil emulsion. This method was previously used and recommended by the author to produce an interstitial nephritis, to influence the blood pressure or an interstitial thyroiditis or pneumonitis etc.

*Influence of Exercise and Pregnancy on A-V Dissociation Due to Sinus Inertia.* F. GROEDEL AND B. KISCH. *Experimental Medicine & Surgery*, 2: 56, February, 1944.

A condition is referred to, that is characterized by a very low and utterly irregular auricular rhythm in a 31 year old patient with a history of severe diphtheria in childhood. The case shows complete dissociation due to the more rapid rate of the ventricular as compared with the auricular rhythm. Some of the auricular beats are followed by ventricular contractions with a a-v conduction time of 0.20-0.225 sec. The condition is designated "a-v dissociation due to sino-auricular inertia." In this case exercise increased the auricular rate and produced a regular a-v sequence with a shortened a-v interval. The same effect as had been obtained after exercise was observed continuously in the latter months of a subsequent pregnancy. Several days after childbirth, the previous pathology returned and has remained until the present date (6 months later). In this case, the effects of exercise and pregnancy on the heart rate are regarded as manifestations resultant from an increased sympathetic tone.

*The Secretion of Gastric Mucus and Hydrochloric Acid in Response to Pilocarpine—A review of the Literature.* F. HOLLANDER. *Gastro-enterol.*, 2: 201, March, 1944.

It is generally believed that pilocarpine stimulates the gastric mucus cells considerably, but the parietal cells only slightly. However, a study recently reported by the author yielded diametrically opposite results and this led to a critical survey of the entire literature on the gastro-secretory activity of pilocarpine. In human subjects, the results have been generally inconsistent, chiefly because of swallowed saliva; hence, decisive studies of pilocarpine action on unoperated humans seem to be impossible. Results with dogs are open to similar objection unless the animals possess gastric pouches, or gastric and esophageal fistulae. Of 27 reports on such animals, 13 gave negative evidence for mucus secretion in response to pilocarpine. Over two-thirds of the investigators reported a considerable volume-output of HCl, even as compared with histamine, whereas, the remainder did not study this factor or reported only small responses. Titrimetric results were even less consistent, and where lowering of the acidity did occur, it was frequently ascribed to neutralization by mucus. Some of the evidence indicated that most, if not all, of this mucus results from the intense motor activity induced by pilocarpine, rather than stimulation of the surface epithelium directly. It is concluded that (1) pilocarpine stimulates directly a copious flow of HCl, pepsin and water; (2) much of the mucus secreted after pilocarpine injection is stimulated secondarily by the gastric contractions; (3) there is considerable doubt whether pilocarpine exercises any direct stimulating action whatever on the mucus cells.

*Depth Dose Measurements for 100-, 120- and 135-kv Roentgen Rays.* C. B. BRAESTRUP. Radiol., 42: 3, 258, March, 1944.

The wide range of depth doses obtained with the four ray qualities used in this study indicates that low- and intermediate-voltage therapy could be carried out more effectively with a limited number of technics. Such simplification would permit better correlation between clinical results and physical factors. Half-value layers of 1.0, 2.0, 4.0, and 8.0 mm. Al. used here, should be sufficient for most clinical purposes. Similarly, two target-skin distances, 15 cm. for small fields (5 cm. or less in diameter) and 30 cm. for large fields, should suffice for the treatment of the majority of superficial lesions.

*Phenomenon of Local Skin Reactivity to Serratia marcescens (B. Prodigiosus). Immunological Relationships between Serratia marcescens Culture Filtrates and Shear Polysaccharide.*

G. SHWARTZMAN. Cancer Research, 4: 191, March, 1944.

Filtrates of cultures of *Serratia marcescens* in a simple synthetic medium, and their concentrates prepared by Shear and his co-workers, are capable of eliciting the phenomenon of local skin reactivity. The phenomenon-producing principles are closely related to or identical with the factors capable of inducing hemorrhages and regressions of mouse tumors. The chemical treatment, including tryptic digestion, employed by Shear and his co-workers for preparation of the product bring about concentration and purification of the active principles of the phenomenon without inducing any measurable alteration in the antigenic specificity as shown by the immunizing value, the precipitation, and the neutralization reactions of the materials.

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THE EDWARD GAMALIEL JANEWAY LECTURES  
 II. RÔLE OF FATS AND CERTAIN OTHER DIETARY  
 COMPONENTS IN VITAMIN E DEFICIENCY\*

HENRIK DAM, Sc.D.

*Associate Member of the Rockefeller Institute for Medical Research*

When, several years ago, my associates and I were studying experimental vitamin K deficiency in chicks we sometimes found a peculiar symptom characterized by the accumulation of fluid in the subcutaneous tissue and fine hemorrhage in the adjacent adipose tissue. In some cases there was also edema and diffuse hemorrhage in the muscles. It was, originally, believed that this condition was a manifestation of the hemorrhagic tendency caused by the lack of vitamin K, but closer examination showed that this is not the case (Dam and Glavind, 1938). The symptom which we called *exudative diathesis* may occur with plenty of vitamin K in the diet and with normal prothrombin in the blood. The first stage of the disease is usually the diffuse hemorrhage in adipose tissue, which frequently can be seen through the skin. Thereafter marked exudation occurs. The protein content of the exudate is about the same as that of blood plasma, and the fluid is usually more or less green colored due to destruction of hemoglobin in the hemorrhagic tissue. The specific gravity of the blood plasma is normal and so is the thromboplastin of the affected tissue; however, the exudate clots on addition of thromboplastin. Marked cases are accompanied by forced breathing. The disease may lead to death or to permanent invalidism through necrotic degeneration of breast and leg muscles, but recovery often occurs spontaneously, sometimes followed by recurrence of the symptom in the same chick without change of the dietary procedure. An augmented capacity of the tissue to take up trypan blue intravenously injected suggests an increased permeability of capillaries in general (Dam and Glavind, 1940).

On the assumption that the disease might be due to the lack of a new vitamin, we began to study the occurrence and general properties of the protective factor. The factor was found in green vegetables, in wheat germ and rose hips; it was fat soluble and occurred in the non-saponifiable fraction. When synthetic alphatocopherol became available, it was easy to show that the factor is vitamin E (Dam and Glavind, 1939).

Later, in 1940, the same disease was found by Bird and Culton using a diet containing a large quantity of skim milk powder and sucrose. Curiously enough, Bird and Culton found the exudates in the peritoneal cavity while we nearly always found them under the skin.

Several years earlier (1931) Pappenheimer and Goettsch had observed another symptom in chicks reared on an artificial diet, somewhat different from the diet

\* Lecture delivered in the Blumenthal Auditorium, The Mount Sinai Hospital, New York, October 31, 1945.

we used. The symptom described by Pappenheimer and Goettsch is the so-called *encephalomalacia*. Chicks suffering from this disease become ataxic and may fall when trying to walk. Frequently they lie on the side with legs stretched or assume a sitting position with the back supported against the wall of the cage. Upon touching violent movements with legs and wings occur. In milder cases, the birds are only slightly ataxic or sit with the body raised and slightly swaying. Forced breathing may be apparent. Localized or diffuse areas of edema, fine hemorrhages and necrosis are usually seen in the cerebellum or the cerebrum. According to Pappenheimer and Goettsch, the cerebellar lesions are characterized histologically by edema, with disorganisation of the fibrillar and granular elements, degeneration of the Purkinje cells and those of the granular layer, small hemorrhages scattered in both white and gray matter, and hyaline thrombosis of capillaries in and around the necrotic areas.

As in the case of exudates, spontaneous recovery with or without recurrent attacks, is common.

Goettsch and Pappenheimer (1936) were also inclined to think that lack of a new fat soluble vitamin was responsible for this symptom, but as soon as pure alpha-tocopherol became available it was shown that the disease is due to the lack of vitamin E (Dam, Glavind, Bernth and Hagens, 1939).

In our experiments on exudative diathesis we often observed encephalomalacia, but exudates were by far the dominating symptom, whereas in Pappenheimer and Goettsch's experiments exudates were very rare. It is therefore clear that lack of vitamin E is not the whole explanation of the two symptoms. There must be some other feature of the diet which determines the way in which the deficiency manifests itself.

We therefore started out to see what changes of the diet may affect the one or the other of the two symptoms. We began with the exudative diathesis. The diet we decided to use for the production of exudates is a little different from the one we used in Copenhagen, since, in the meantime Almquist and his associates had shown that chicks need for growth a higher amount of glycine in their diet than that which is provided in 15 per cent of casein. We therefore give extra 8 per cent of gelatin. Almquist and his group had also shown that the growth of chicks is accelerated by glucuronic acid and some related compounds which can be furnished in the form of 5 per cent gum arabic.

In the first tests, the salt mixture was the same as the one previously used, viz., 2 per cent of a mixture consisting of  $\text{CaCO}_3$ ,  $\text{MgCO}_3$ ,  $\text{NaCl}$ , Ferric citrate + traces of Cu and Mn and a still smaller trace of iodine in the form of diiodotyrosine. Such a diet is low in salts and the phosphate is furnished only in the form of casein and yeast. It appeared at once that the chicks reared on this diet did not develop the disease very easily. Then we tried to use another salt mixture, similar to the one which Pappenheimer and Goettsch had used, viz., McCollum's salt mixture 182 with added Cu and Mn, the latter to prevent perosis. Pappenheimer and Goettsch used 7.2 per cent of the salt mixture in their diet, when calculated without the roughage. So we also used 7.2 per cent which is a rather high amount. The result was that the exudates came much

earlier and were more marked. The next step was to add NaCl to the low salt diet to see if extra NaCl was enough to accelerate the exudates. This was actually the case. If, instead of NaCl, KCl was used, no such accelerating effect on the symptom was observed; on the contrary, there was rather a retarding effect. This is in agreement with the clinical experience that a tendency to edema is enhanced by NaCl and to some extent minimized by potassium salts. After this fact was established regarding the exudative diathesis (Dam and Glavind, 1942), we always used a salt-rich diet with 7.2 per cent of the fortified McCollum's salt mixture.

Comparison between ether-extracted and unextracted yeast showed that the symptoms appeared sooner when the yeast was extracted. This may be due to a trace of tocopherol in the yeast or to some other substance which protects vitamin E from destruction (as suggested by Patrick and Morgan, 1943).

Next we tried to use different carbohydrates in the diet. Sucrose, starch, glucose or fructose could be used with equal result. In the case of lactose and galactose there are complications since chicks cannot digest a large amount of lactose and cannot metabolize properly large amounts of galactose (H. Dam, 1944d).

The protein-carbohydrate ratio is of importance. Lowering of the casein to 7.5 per cent and correspondingly increasing the carbohydrate (starch) gave a somewhat slower development of the exudates, perhaps because of the slow growth on the low protein diet, but increase of the casein to 35 per cent delayed and minimized the incidence of the symptom very much, even though growth was somewhat improved, by the increase of protein. Whether the effect on the tendency to exudation is actually due to the increase in protein rather than to the decrease in carbohydrate is not yet decided.

The occurrence of the symptoms is not confined to casein diets. Alcohol-extracted meat meal can also be used. It seemed that ether-extracted dehydrated chicken egg white was unfavorable for the development of the symptoms. The reason for this is not clear. One could think that the symptoms had some relation to a species-foreign protein but this seems not to be the case since the addition of small amounts of casein, say 2 per cent, to the egg white diet did not speed up the symptom.

We now come to the most important factor besides the lack of vitamin E namely, the type of fat in the diet. Indications that the ingestion of certain fats such as cod liver oil will accelerate certain vitamin E deficiency symptoms were already on hand when this research began, namely, as far as the muscular dystrophy in rabbits and guinea pigs is concerned. It was, however, believed that this effect was due to destruction of traces of vitamin E in the food through rancidity of the cod liver oil. Mackenzie and Mackenzie showed that muscular dystrophy could just as well be produced by means of a fat free diet deprived of vitamin E.

In our case of exudative diathesis and encephalomalacia in chicks, we found a much more striking effect of certain fats as we shall see in the following (Dam, 1943, 1944).

The diet we commonly used for the production of exudates contained 5 per cent cod liver oil. We now tried to give the same diet without cod liver oil or with various other fats instead of cod liver oil in the same amount. The result was that without cod liver oil no symptoms appeared whereas with lard they developed slower than with cod liver oil. If the cod liver oil content was increased to 20 per cent, the exudate came fast and most animals died from severe exudation.

A closer examination showed that without added fat, exudates—very mild ones—appeared only in 3 out of 100 chicks, whereas with 5 per cent cod liver oil about 90 out of 100 showed the symptom within the experimental period of 35 days.

The next step was to oxidize the cod liver oil to varying degree before it was given to the animals. In one experiment cod liver oil was heated on a steam bath for 24 hours with air bubbling slowly through it, whereby the iodine value fell from 173 to 149. The cod liver oil thus altered produced the symptoms to about the same degree as fresh cod liver oil. When the cod liver oil had been heated in the same way for one week whereby the iodine value fell to 86, it had completely lost its power to produce symptoms, and the same was the case when the cod liver oil was made rancid in the diet by standing on shallow trays at 50°C. for one week whereby the iodine value fell to 62.

This is not in agreement with the assumption that the effect is due to destruction of a trace of vitamin E in the diet through the rancidity.

One might think, though, *a priori*, it does not seem very likely, that the rancidity had produced a protecting substance in analogy with the known fact that in the case of vitamin K deficiency, putrefaction produces a substance which protects against the disease. It is easy to show that this is not the case in the present type of experiment, since addition of fresh cod liver oil to the diet containing rancid cod liver oil produces the symptoms as if no rancid cod liver oil were present. These observations suggest that it is the fatty acids in cod liver oil which produce symptoms when no vitamin E is given. They also suggest that it is the highly unsaturated fatty acids which are responsible. This assumption is entirely borne out by experiments which I shall mention a little later.

So far we have mainly considered the exudative diathesis, although in most of the experiments some cases of encephalomalacia accompanied the exudates, and was suppressed by the same dietary measures which prevented exudates. Encephalomalacia has never been observed with fat free diets. Pappenheimer and Goettsch's diet which gives encephalomalacia and very rarely exudates contains a rather high amount of casein, viz., 22 per cent + the amount contained in the skimmed milk powder, which makes a total of about 30 per cent. The content of carbohydrate (starch) is moderate, 22 per cent. The lactose from the skim milk powder is poorly digested by chicks and can probably be left out of consideration. In addition to this, the diet contains a considerable amount of lard, 23 per cent, and only 2.2 per cent of cod liver oil.

We then prepared a diet which exceeded Pappenheimer and Goettsch's diet

with respect to high casein, low carbohydrate and high lard content. We increased the casein content in our usual exudate producing diet from 15 per cent to 35 per cent, added 35 per cent lard, and gave no carbohydrate other than that which was present in the yeast. The result of this was mild encephalomalacia with no exudates. Even if we leave the casein content at 15 per cent, give 25 per cent starch and 30 per cent lard (Vitamins A and D as concentrates twice a week), the main symptom is marked encephalomalacia although some exudates develop later than the encephalomalacia. On the high lard diet, a high protein carbohydrate ratio will tend to shift the symptom toward encephalomalacia and the absence of carbohydrate makes the encephalomalacia milder.

There is, however, another way to develop encephalomalacia as the main symptom, that is by giving hog liver fat instead of cod liver oil.

Before we proceed to a discussion of the effects of the different components of the fats, we may briefly consider what happens when certain lipotropic substances are added to the diets. First we increased the amount of choline to 1 per cent. This had no effect whether the diet was the usual exudate producing diet or the encephalomalacia producing high lard diet. Tests with choline-free diets could, at that time, not be carried out because folic acid was not available, and therefore the chicks did not thrive at all on a diet with synthetic B-vitamins. Two other lipotropic substances, inositol and lipocaic, have a definite effect on the symptoms. If 1.5 per cent of inositol is added to either of the two diets, both exudates and encephalomalacia will be delayed and their incidence decreased. If instead of inositol 2 per cent of lipocaic is added, exudates will be cut down but there is no effect on encephalomalacia. The lipocaic preparation we used was put at our disposal by Dr. Dragstedt of the University of Chicago. The effect of lipocaic on the symptoms cannot be due to vitamin E contained in the preparation as an impurity since the Emmerie Engel test failed to reveal the presence of vitamin E in the preparation. The effect is probably related to the influence of these lipotropic substances on the metabolism of fats. Some support for this assumption lies in the observation that on the artificial diets used both vitamin E and lipocaic depress the ratio phospholipids: total lipoids of the blood plasma, though this ratio is still different from that which prevails when a natural diet is used. Regarding the effect of inositol it is worthwhile to remember that Milhorat and Bartels have reported that an inositol-ester of tocopherol has a higher biological effect than tocopherol itself.

We will now consider the effect of various fractions of the fat in the diet.

We start with a control diet which has neither vitamin E nor any added fat. This diet gives no symptoms within the 35 days of the experiment.

If 5 per cent cod liver oil is added, the symptoms come as usual after a couple of weeks.

With the non-saponifiable fraction of cod liver oil, given in an amount equivalent to 5 per cent cod liver oil no symptoms come, but with the fatty acids from 5 per cent cod liver oil, freed from the non-saponifiable, the symptoms (mainly exudates) come even more pronounced than with the cod liver oil itself.



The fatty acids from linseed oil have an effect similar to but less than that of cod liver oil. Pure oleic acid has no effect at all.

With hog liver fat only encephalomalacia appeared, and with the equivalent amount of hog liver fatty acids encephalomalacia came faster and more pronounced than with the fat itself, but there were also some cases of exudate. Hog liver fatty acids gave some intrapericardial exudates, rarely seen with cod liver oil.

These experiments show clearly that the acceleration of the symptoms is due to the fatty acids.

Next we make fractions of varying degree of unsaturation from the fatty acids of hog liver fat (Dam, 1944b). The fractionation is made according to the method of Brown and Stoner (1937), viz. by crystallisation from an acetone solution of the fatty acids at different temperatures. By cooling the solution to  $-20^{\circ}\text{C}$ . a fraction crystallizes which mainly consists of saturated acids (iodine value about 4). By cooling the filtrate further, to  $-74^{\circ}\text{C}$ . or  $77^{\circ}\text{C}$ . (the lowest temperature obtainable with dry-ice) a moderately unsaturated fraction comes out (i.v. 90). What remains in acetone solution at this low temperature is highly unsaturated (i.v. 242).

When each of these fractions was tested in an amount of 4 per cent of the diet (no cod liver oil) it was found that the largely saturated fraction gave only a few cases of exudate. The middle unsaturated, gave both exudates and encephalomalacia; and fraction 3, the highly unsaturated, killed all the animals through encephalomalacia within a short time, most of them within 2 weeks. Only a few and mild cases of exudates were found in this group, that is redness of the fat tissue, without any grossly visible exudation.

When a much smaller amount of the highly unsaturated fraction was given, an amount corresponding to 0.5 per cent of the diet, the result resembled that obtained with 4 per cent of the middle fraction.

These experiments show beyond any doubt that it is the highly unsaturated fatty acids which are responsible for both symptoms, and that the result is dependent upon the amount of the unsaturated fatty acids ingested.

A suitable dose of d,l-alpha-tocopherol acetate can prevent all the symptoms, including the very drastic effects of fraction 3.

The question now arises: In what way do the highly unsaturated fatty acids provoke the symptom?

Sinclair (1932) has shown that dietary highly unsaturated fatty acids are deposited in the body phosphatides of rats. It is also known that such fatty acids go into the fat depots. Determinations of iodine values of the phosphatides in muscle, liver and brain of chicks fed cod liver oil confirm that highly unsaturated fatty acids are deposited in these tissues, although to a lesser extent in brain. There is no difference in iodine value between the series of animals fed vitamin E together with the cod liver oil and those fed cod liver oil without vitamin E. Nevertheless there can scarcely be any doubt that both the presence of the highly unsaturated fatty acids in the tissue and the absence of dietary vitamin E are pre-requisite to the development of the symptoms. If, under

different dietary conditions, highly unsaturated fatty acids accumulate to a different extent in the various tissues, this would give an explanation of the variation of the location of the symptoms. This has, however, not yet been proven directly.

The simplest explanation of the effect of the unsaturated fatty acids would be that these fatty acids oxidize in an abnormal way in the tissue when vitamin E is absent, and that the abnormal oxidation products cause the symptoms by damaging the tissue.

As far as the adipose tissue is concerned, it is particularly easy to take out a piece, extract the fat and determine the presence of peroxides. Chicks receiving normal diets or control diets with vitamin E have no peroxides in their body fat, but in chicks receiving the exudate producing diet, peroxidation of the body fat is just detectable at the time when symptoms begin to appear, but far below the limit for rancidity accepted for industrial fats (20 milliequivalents per 100 gm. of fat). In one case with severe hemorrhage in the adipose tissue, no peroxides could be determined at all. If the symptoms are not caused by the first stages of abnormal oxidation of the fat in the tissue involved, the beginning peroxidation may at least be a sign of the simultaneous exhaustion of vitamin E and the accumulation of certain fatty acids, which for some other reason is incompatible with the normal constitution of the tissue. Later, that is, after the hemorrhage and exudation has ceased, the fat tissue often shows a brown color. This brown color is often associated with higher peroxide values in the fat which may in some cases exceed the rancidity limit (20). Subcutaneous injection of cod liver oil in normal chicks leads, in a few days, to very high peroxide values of the injected oil (about 200) but this does not produce hemorrhage or exudate; it produces, however, some brown fibrous tissue on the spot where the cod liver oil was injected. If therefore the beginning peroxidation is the cause of the hemorrhage and exudation from the tissue, it must apparently occur within the cells which are going to be affected.

It would be interesting to find out whether the exudative diathesis and encephalomalacia can be produced in other species of animals than chicks.

Pappenheimer and Goettsch (1934) reported that the diet which produces encephalomalacia in chicks will produce muscular dystrophy in ducklings within 33 days. When we gave our usual exudate-producing diet to ducklings, it produced a general weakness but no exudate and no definite changes of the muscles within the same length of time as was used in Pappenheimer and Goettsch's experiments. Therefore, variations of both diet and species may give different results.

Several experiments have been made to produce exudate and encephalomalacia in rats, but the symptoms did not appear. However, a brown coloration of the adipose tissue developed when rats were given vitamin E deficient diets with high cod liver oil. With 20 per cent cod liver oil in the diet this symptom became very marked. The brown color did not appear when 10 mg. per cent of d,l-alpha-tocopherol acetate was given in the diet or when no cod liver oil was given.

The pigment of the discolored adipose tissue consists of two components, one of which is fat soluble while the other is not. The non-fat soluble components seems to be the major constituent. It is extractable with 2 per cent NaOH at room temperature and is precipitated with acids together with protein decomposition products. It cannot be brought into solution in fat solvents even after its alkaline sol. has been hydrolyzed by heating with alkali. It does not give reactions for melanine and does not contain iron. Its color is stronger in alkaline solution than when it is precipitated by acids. Both compounds, the fat soluble and the non-fat soluble, give a yellow-green fluorescence under the ultraviolet lamp. The fat-soluble component is probably the same as that which is responsible for the brown coloration of oxidized cod liver oil or of oxidized cod-liver-oil-fatty-acids. It seems likely that the development of this pigment is due to an unphysiological oxidation of glycerides of highly unsaturated fatty acids from cod liver oil occurring in fat depots which do not contain enough anti-oxidant to prevent such an oxidation. In fact, the fat of rats which showed a marked color of their fat depots, had peroxide values, in most cases far above the limit for rancidity (Dam and Granados, 1945).

The brown discoloration of adipose tissue develops particularly fast and the peroxide values become particularly high (over 100) when the rats are given the experimental diet from birth, that is: when they are left with their mothers on the diet from the time of delivery. This may be due to transmission of the particular fatty acids through the milk although the young rats will begin to eat of the diet from about the end of the 2nd week. It may also be due to a particular sensitivity of the young adipose tissue to the effects of cod liver oil fatty acids given without vitamin E.

The pigment of the discolored adipose tissue resembles "ceroid" a pigment described for instance by Endicott and Lillie 1944 and by Gyorgy and Goldblatt, 1942. Ceroid occurs in the liver, lymph nodes and various other tissue of rats suffering from experimental liver cirrhosis due to low choline and methionine. Ceroid has mainly been characterized by its histological staining reactions and by its yellow-green fluorescence under the ultraviolet lamp. When I gave the brown colored adipose tissue to Dr. Mason for histological examination, it appeared that he had some old slides from muscles of vitamin E deficient animals which had shown a similar brown color in the later stages. Both the discolored adipose tissue, the brownish muscle tissue and ceroid from nutritional liver cirrhosis show granules which stain acid fast with fuchsin and give a yellowish-green fluorescence. It is likely that all 3 pigments are identical, and have a common origin. Endicott (1944) suggested that his ceroid is related to the oxidation of unsaturated fatty acids and he reported a local ceroid formation after intramuscular or subcutaneous injection of cod liver oil or linseed oil; on the other hand, ceroid did not develop in experimental liver cirrhosis when no fat was given. Endicott's findings concerning the pigment of liver cirrhosis are in good agreement with ours concerning the discolored adipose tissue.

The high cod liver oil vitamin E deficient diet gives rise to another easily detectable symptom in rats, viz., prevention of the normal pigmentation of the

incisors (Granados and Dam, 1945). Normally the frontal surface of the incisors is yellow-brown due to a pigment in the outer surface of the enamel. The high cod liver oil vitamin E deficient diet causes this pigment to disappear. Davis and Moore (1941) found this influence of lack of vitamin E but were not aware of the rôle of fat. The incisors of rats grow steadily also in the adult animal. Under the abnormal dietary regime, the formation of the pigment is stopped and the tooth grows out colorless. Lard will also stop the formation of the pigment although it does not cause discoloration of the adipose tissue such as cod liver oil does. The effect is particularly striking as far as the upper incisors are concerned, while the lower incisors are affected to a lesser extent and more slowly.

The fact that it is the highly unsaturated fatty acids which produce both the coloration of the adipose tissue and the depigmentation of the incisors appears from the following simple tests (Dam and Granados 1945).

The non-saponifiable fraction of cod liver oil has no effect in producing either of the two symptoms when given in an amount equivalent to 20 per cent cod liver oil in the diet, whereas the fatty acid fraction has. Fractionation of the fatty acids after Brown and Stoner (1937) into 3 fractions of varying degree of unsaturation and testing them separately shows that the effect is connected with the highly unsaturated fraction (of iodine value 283) while there is very little effect with the middle fraction (iodine value 99) and none with the largely saturated fraction (iodine value 13).

The pigment of the incisor enamel is quite different from that of the discolored adipose tissue. It does not fluoresce and it contains iron in the ferric form. When no pigment is formed the incisor enamel shows no reaction with Potassium ferri or ferro cyanide after incineration and solution in dilute HCl. The high cod liver oil vitamin E deficient diet probably interferes with the function of the ameloblasts in such a way that this organ cannot deposit the normal iron containing film on the outer surface of the incisor enamel.

It has also been tried whether it is possible to produce exudates in rats fed a vitamin E deficient cod liver oil containing diet by drastically lowering the protein content of the diet (Dam, 1944c). This was done by omitting the casein from the diet after a certain length of time so that the only source of protein was the 10 per cent of dried yeast. This did not cause exudation, but another observation was made, viz., that rats which received vitamin E in the form of d,l-alpha-tocopherol acetate (10 mg. per 100 gm. of diet) survived somewhat longer on the low protein diet than did those which were not given vitamin E. The explanation of this observation is not quite clear.

Since vitamin E deficiency may influence at least part of the vascular system, namely, the capillaries, and since it has been found that the muscles of vitamin E deficient animals are richer in cholesterol than muscles of animals fed vitamin E (Morgulis et al., 1938, Heinrich and Mattill, 1943, Dam, 1944), it seemed of interest to investigate the question whether the presence or absence of vitamin E might not influence the deposition of cholesterol in the aorta of animals fed a diet rich in cholesterol.

Such an investigation has been carried out with rabbits and chicks. For rabbits a basal diet was used which in itself was not adequate for normal growth and not free from vitamin E. It consisted of ground oats + a trace of vitamin K and 50 gms. of carrot per day. To each 100 gm. of the oats diet was added 1 gm. of cholesterol with or without simultaneous addition of 10 mg. d,l-alpha-tocopherol acetate. The animals were kept on these diets for about 3 months. The animals on the high cholesterol diet which was not supplemented with synthetic vitamin E died much faster than those on the basal diet; those which received both cholesterol and synthetic vitamin E had a lower mortality than the two other groups. From the animals which survived for 3 months, the aorta was taken out for cholesterol determination. Enhanced cholesterol values were found in the two cholesterol fed groups, also in the one which received vitamin E.

In a similar experiment with chicks the basal diet was vitamin E deficient and contained 30 per cent lard. In some groups this diet was supplemented with 10 mg. per cent ephynal acetate, or 2 per cent cholesterol, or both. In the vitamin E deficient groups several of the animals died of exudates and encephalomalacia (in the cholesterol group only from exudates) whereas in the vitamin E supplemented groups all animals were alive after 61 days. The surviving animals were killed at this age. Those which had had 2 per cent cholesterol in their diet had about 3 times as much cholesterol in their aortas as those which received no added cholesterol. And the addition of synthetic vitamin E did not alter the result. It was also tried in some groups to add 1.5 per cent inositol or 2 per cent lipocaic to the cholesterol diet which also had vitamin E. These additions did not influence the cholesterol deposition in the aorta either (Dam, 1944a). Another worker (M. Bruger, 1945) has found that vitamin E injection increased the deposition of cholesterol in the rabbit aorta when these animals were fed diets with 1 per cent cholesterol.

With the data available it is scarcely possible to say how this difference is to be explained, but at least the results agree as far as the non-effectiveness of vitamin E in counteracting experimental arteriosclerosis is concerned.

In addition, it can be said that vitamin E gives some protection against the effects of low protein and high cholesterol as far as the substance seems to keep the animals alive longer, but the protection against the effects of highly unsaturated fatty acids is far more striking.

An investigation was conducted (Glaser and Dam, 1944) to determine whether high doses of vitamin E (250 mg. ephynal acetate per day) would influence Ragweed pollinosis in patients. This experiment was carried out because of the observed influence on capillary permeability in chicks. The effect in Hayfever patients was entirely negative.

The experiments described so far leave no doubt that vitamin E exerts an influence on the way in which fats are handled in the animal body. They also suggest that the antioxidant effect of vitamin E is a factor in the protection against certain vitamin E deficiency symptoms, but future research will have to clear up the exact nature of the mode of action of the vitamin.



## BIBLIOGRAPHY

- DAM, H., AND GLAVIND, J.: *Nature*, 142: 1077, 1938.  
———: *Ibid*, 143: 810, 1939.  
———: *Skand. Arch. Physiol.*, 82: 299, 1939.  
———: *Naturwissenschaften*, 28: 207, 1940.  
———: *Science*, 96: 235, 1942.  
———, BERNTH, O., AND HAGENS, E.: *Nature*, 142: 1157, 1938.  
———, PRANGE, I., AND OTTESEN, J.: *Kg. Danske Videnskabernes Selskab. Biologiske Meddelelser*, 16: 7, 1941.  
———, AND KELMAN, E. M.: *Science*, 96: 430, 1942.  
———: *Proc. Soc. Exp. Biol. & Med.*, 52: 285, 1943.  
———: *J. Nutrition*, 27: 193, 1944.  
———: (a) *Ibid*, 28: 289, 1944.  
———: (b) *Ibid*, 28: 297, 1944.  
———: (c) *Proc. Soc. Exp. Biol. & Med.*, 55: 55, 1944.  
———: (d) *Ibid*, 55: 57, 1944.  
———, AND GRANADOS, H.: *Acta Physiologica* (in press), 1945.  
———: (a) *Science*, 102: 327, 1945.  
———, AND MASON, K. E.: *Federation Proceedings*, 4: 153, 1945.  
GLASER, J., AND DAM, H.: *J. Allergy*, 15: 18, 1944.  
GRANADOS, H., AND DAM, H.: *Science*, 101: 250, 1945.  
———: (a) *Proc. Soc. Exp. Biol. & Med.*, 59: 295, 1945.  
BIRD, H. R., AND CULTON, T. G.: *Proc. Soc. Exp. Biol. & Med.*, 44: 543, 1940.  
GOETTSCH, M., AND PAPPENHEIMER, A. M.: *J. Biol. Chem.*, 114: 673, 1936.  
PAPPENHEIMER, A. M., AND GOETTSCH, M.: *J. Exp. Med.*, 53: 11, 1931.  
———: *Ibid*, 59: 35, 1934.  
———, AND JUNGHER, E.: *Storrs Agric. Exp. Sta. Bull.*, 229, 1939.  
MACKENZIE, C. G., MACKENZIE, J. B., AND MCCOLLUM, E. V.: *J. Nutrition*, 21: 225, 1941.  
MATTELL, H. A., AND GOLUBIC, C.: *J. Nutrition*, 23: 625, 1942.  
HEINRICH, M. R., AND MATTELL, H. A.: *Proc. Soc. Exp. Biol. & Med.*, 52: 344, 1943.  
PATRICK, H., AND MORGAN, C. L.: *Science*, 98: 435, 1943.  
SINCLAIR, R. G.: *J. Biol. Chem.*, 96: 103, 1932.  
ENDICOTT, K. M., AND LILLIE, R. D.: *Am. J. Pathol.*, 20: 149, 1944.  
GYORGY, P., AND GOLDBLATT, R.: *J. Exp. Med.*, 75: 355, 1942.  
ENDICOTT, K. M.: *Arch. Pathol.*, 37: 49, 1944.  
DAVIES, A. W., AND MOORE, T.: *Nature*, 147: 694, 1941.  
BROWN, J. B., AND STONER, G.: *J. Am. Chem. Soc.*, 59: 3, 1937.  
MILHORAT, A. T., AND BARTELS, W. E.: *Science*, 101: 93, 1945.

## OBSERVATIONS ON TWO CASES OF HUMAN FILARIASIS (*WUCHERERIA BANCROFTI* AND *MANSONELLA OZZARDI*)

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*From the Second Medical Service*

There are few organisms so hardy and so resistant to medication as the filariae. Although assailed on numerous occasions by some of the most potent as well as the most toxic drugs used on human beings, they still constitute an unsolved therapeutic problem.

A list of the drugs used against filariasis incorporates almost all the known parasiticides: sulfanilamide (1), prontosil (2), arsaminol (3), fuadin (4), gold (5), trypaflavine (6), tartar emetic (7), arsphenamine (10), hectine (11), thymol (12), parenteral carbon tetrachloride (13), and picric acid (14). An especially extensive study was conducted by Chopra and Rao in 1939 (15). These investigators gave painstaking and exhaustive clinical trial to 76 different drugs, many of which had been favorably reported on before. They used antimony, arsenic, gold, mercury, copper, zinc, tin, lead and iodine compounds as well as 40 organic drugs. With none of these drugs were they able to demonstrate any significant therapeutic effect. A similar result was obtained in a more limited study by Hawkins (16).

Particular attention has been given to the antimony compounds because of their effectiveness in schistosomiasis and kala-azar. However, fuadin has consistently failed when tried in human filariasis. It is widely used against dirofilariasis immitis in dogs, although the experimental evidence is hardly favorable. Even when sufficient fuadin was given to kill the dog, live parental filariae were still found in the heart, the parasite apparently tolerating the drug better than the dog (4, 17).

Recently anthiomaline, another antimony compound, has been tried extensively. In the treatment of kala-azar this antimony compound has been proved to be much less efficient than fuadin. Even so, anthiomaline has been reported to give suggestive results in the treatment of human filariasis (18). The reports published until now indicate that the drug at best seems to be of limited merit.

Consequently, in two cases of filariasis observed here, it was felt that two methods of therapy hitherto not tried in this disease might be justified.

### CASE REPORTS

*Case 1. History and Clinical Course:* A 20-year old Dutch mariner born in Paramaribo, Dutch Guiana, was referred to Mount Sinai Hospital because in a routine stool analysis, eggs of *Schistosoma mansoni* had been found. Diffuse spongy enlargement of the inguinal lymph nodes was felt bilaterally. There was on the left a smaller hydrocele containing approximately 15 cc. of fluid. The liver and spleen were not palpable and there were no other significant findings. The blood count showed 7 per cent eosinophilia, but was otherwise entirely normal. Urinalysis and chest x-ray were similarly not remarkable.

Active microfilariae of *Wuchereria bancrofti* were discovered in the hydrocele fluid and the blood stream. By both the thick drop method of Brown and Sheldon (19) and by direct

examination of fresh blood or serum, the filaria count varied from 1-3 per 0.1 cc. Stool examination showed innumerable ova of *Trichuris trichiuris*, *Oxyuris vermicularis*, *Necator americanus*, and occasional ova of *Schistosoma mansoni*. These findings confirm the well-known fact that in the Guianas, on the east coast of the northern part of South America, multiple parasitic infestations are common.

After a short period of observation, 25 mgm. of stilbamidine<sup>1</sup> were given intravenously. The dose was gradually increased each day until 150 mgm. per injection was given. The usual precautions of preliminary administration of adrenalin, frequent blood pressure determinations during the injection, and very slow administration, were observed. The patient complained of "needles sticking into his body" during the course of the injection but felt perfectly well afterwards. Shortly after the first administration of the full dose of 150 mgm. he became very faint. This passed over in less than a minute. The dose was reduced to 110 mgm. and administered without incident until a total of 1.2 grams had been given. Urinalysis and blood counts during this period showed no significant change. Blood examination undertaken nightly demonstrated no depreciation in the number of filariae. Final examination, ten weeks after the end of the period of therapy, showed a count identical with that before treatment was started. The intestinal parasites seemed to be similarly unaffected.

*Comment:* Recently Laurie and Yorke (20), while investigating the activity of certain aromatic amines against trypanosomas in vitro, found that 4-4' diamidino stilbene was the most effective drug tested. Shortly thereafter, Devine (21), using laboratory animals, demonstrated that while this drug showed an immediate depressor action, no pathological changes in the viscera occurred after repeated administration of large amounts. Napier, Gupta and Sen (22) treated 100 patients suffering from Indian kala-azar with this drug and reported 98 cures. No dangerous toxic effects were observed but anesthesia in the area of the second division of the trigeminal nerve not infrequently developed after the treatment had been terminated. Good results have also been reported in the treatment of Sudanese kala-azar (23) and in trypanosomiasis (24). As some compounds containing antimony allegedly have a therapeutic influence upon infections with filariae, it was felt that stilbamidine, which, like antimony, has a curative influence on kala-azar, deserved a trial in filariasis.

The reactions to the stilbamidine injections noted in our case were not alarming and seemed entirely dependent upon the dose and speed of injection. No abnormalities in blood count or urine occurred during the period of treatment. The status of the filariasis, as well as the status of the schistosomiasis, however, was not apparently affected by this drug.

*Case 2. History and Clinical Course:* A 27-year-old Negro was referred to this hospital<sup>1</sup> for treatment of intestinal parasites. He was born on the island of Guadeloupe. Until 1940 he had never left the island, although for ten years he worked in a small boat that navigated its coastal waters. A number of months after the fall of France he left his home and stayed for five months on the small British island of Dominica.

On board a French vessel in the North Atlantic, he suffered a scratch of the abdominal wall which subsequently became infected. This led to a medical consultation in New York and admission to this hospital.

Physical examination showed a small infected abrasion on the anterior abdominal wall.

<sup>1</sup> 4-4' diamidino stilbene, May & Baker Ltd., Dagenham, England.

There was moderate diffuse lymphadenopathy, the glands being small and hard. The spleen and liver were not palpable. There was no hydrocele or edema. The blood count and smear showed no abnormality other than an eosinophilia of 7 per cent. Chest plate and urine analysis were not remarkable. The stool showed innumerable ova of *Oxyuris vermicu-*

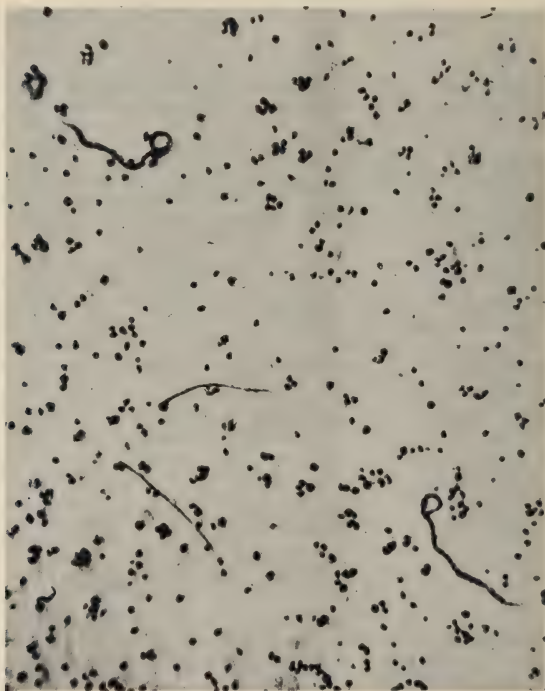


FIG. 1. Low power magnification demonstrating two microfilariae, *Wuchereria bancrofti* and *Mansonella ozzardi*. The former may be recognized by its curves and its sheath; the latter by the straight position in which it is usually found, and by the absence of a sheath.

*laris*, *Trichuris trichiuris*, *Ancylostoma duodenale*, and occasional ova of *Schistosoma mansoni* and *Strongyloides stercoralis*.

A blood smear taken at night showed that this patient was suffering from a double infection with two different kinds of filariae (fig. 1). In a native preparation, apart from the well-known microfilariae of *W. bancrofti*, a thinner microfilaria could easily be discovered. The latter microfilaria moved much more suddenly and whip-like than the smoothly moving, coiled-up, *W. bancrofti* embryos. Stained smears were prepared in the following way. A small quantity of the uppermost layers of the plasma which collected when citrated blood

was left standing for about thirty minutes, was diluted with ten times its volume of 2% formalin. The mixture was centrifuged and smears, made of the precipitate, were stained with Wright's stain. Coiled up microfilariae of *W. bancrofti* with a thick sheath and a thin

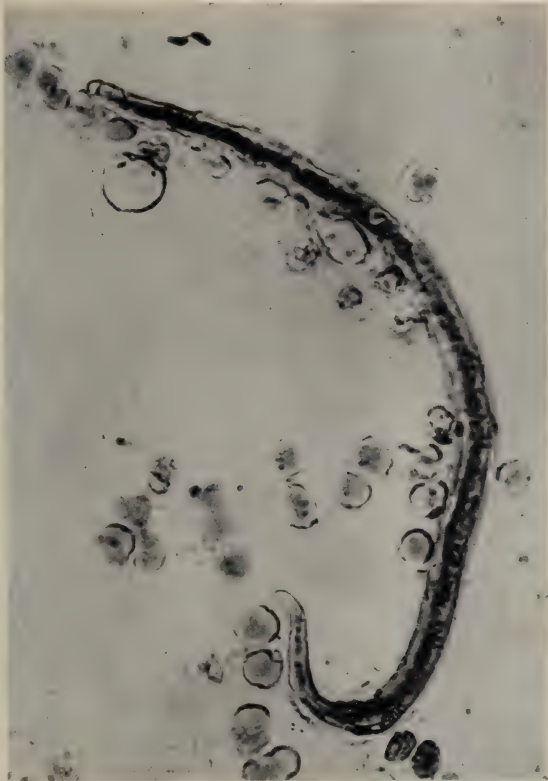


FIG. 2. *Wuchereria bancrofti*. This microfilaria is characterized by a sheath, a blunt head, and by the absence of nuclei in the terminal portion of the tail.

tail without nuclei could easily be identified (fig. 2). In addition there were numerous thinner microfilariae, usually perfectly straight, without a sheath, and also with a pointed tail without nuclei (fig. 3). These characteristics indicated that the latter microfilariae were the embryos of *Mansonella ozzardi*. (Synonyms: *Microfilaria demarquayi* and *Mf. tucumana*). This was confirmed by the position of anal pore, excretory cells and nerve



ring. - Finally, it appeared that in contrast with the microfilariae of *W. bancrofti*, the thin microfilariae could be demonstrated not only in night but also in day blood; this absence of periodicity is characteristic for the *Mansonella ozzardi*.

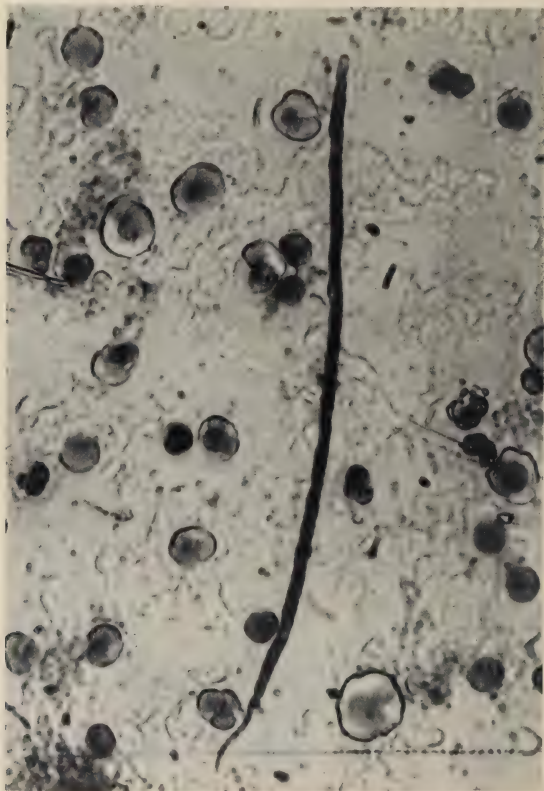


FIG. 3. *Mansonella ozzardi*. In this microfilaria there is no sheath; the tail is sharp; and the nuclei do not extend to the tip of the tail.

Even at night the microfilariae of *Mansonella ozzardi* were present in much larger quantities than the embryos of *W. bancrofti*. A blood smear taken at night showed a filarial count of 64 in 0.1 cc. of blood. There were 56 *Mansonella ozzardi* and eight *Wuchereria bancrofti*. The relative numbers varied considerably with the time of examination.

After a short period of observation a continuous intravenous drip of gentian violet was administered for six days. During the first three days the patient received 75 mgm. daily; for the following two days he received 150 mgm. daily, and for four days 300 mgm. daily. After about 24 hours of this treatment his temperature mounted to 101°F., and the eosinophile count to 17 per cent. The temperature and the eosinophile count returned to their previous levels on the fourth day.

The patient stated that everything appeared violet to him. Nevertheless his sclerae did not become purple. His urine did not become purple nor did his serum. Repeated urinalyses proved to be normal, as were the blood counts, other than for the transient rise of eosinophiles.

Repeated microfilaria counts showed a progressive decrease; this decrease, however, was only in the ranks of the *Mansonella ozzardi*. A number of counts after cessation of therapy showed a general average of four *Mansonella ozzardi* and eight *W. bancrofti* in 0.1 cc. of blood. A later count taken one month after cessation of therapy showed the same concentration and relative proportions.

*Comments:* *Mansonella ozzardi* has been reported from British and Dutch Guiana, the British West Indies, Colombia, northern Argentina, Bolivia, Yucatan, Puerto Rico, Panama and Venezuela. The adult worm is said to live in the mesentery and the visceral fat. The presence of *Mansonella ozzardi* does not give rise to clinical signs.

It is of interest to note that this man had spent almost all of his life on the island of Guadeloupe, an area from which *Mansonella ozzardi* has not been previously reported. On the island of Dominica, on the other hand, upon which he spent five months, George Low (25) discovered a number of cases of *Mansonella ozzardi* as well as a much larger number of *Wuchereria bancrofti* infections. It is impossible to decide whether our patient was infected on the island of his birth or in Dominica. A sojourn of five months in Dominica must be considered sufficient to acquire an infection of *Mansonella ozzardi*. This is indicated by a report from northern Argentina where a child, six months old, was found to carry the microfilariae of this worm in its blood (26).

Gentian violet is a well-known and widely accepted parasitocidal agent. It has been used with success against a number of intestinal parasites (27). Ashford and Snyder report slight but probably insignificant therapeutic results against *Wuchereria bancrofti* when used orally in small doses (8).

The intravenous use of this drug is by no means new. In the last few years preceding the advent of the sulfonamides, desperate efforts to find a drug effective in subacute bacterial endocarditis and in general sepsis led to widespread clinical trials of gentian violet (28, 29, 30, 31). Several of these reports were not unfavorable. The only serious toxic effect was immediate syncope. The dose most frequently used was 5 mgm. per kilo repeated after three days.

Churchman (32) had previously shown that rabbits treated intravenously with very large doses of gentian violet did not develop organic changes in the viscera.

The initial response of our patient to the drug was an elevation of temperature and a definite increase in the percentage of eosinophiles in the blood film. It was felt that this might possibly be due to the death of the parental filariae, and subsequent blood examination showing a decrease in total microfilarial counts

appeared to bear this out. Nevertheless it soon became apparent that only *Mansonella ozzardi* were being destroyed, an accomplishment of no importance since these are essentially non-pathogenic. The absolute *Wuchereria bancrofti* count did not significantly change. In addition, the parasitic ova noted in the stool on admission were also present at the end of the period of treatment.

#### CONCLUSIONS

Stilbamidine produced no decrease in the number of circulating microfilariae in one case of *Wuchereria bancrofti* infection.

A double infection with *Wuchereria bancrofti* and *Mansonella ozzardi* was observed in a native of Guadeloupe who, however, had lived for five months in the island of Dominica, where *M. ozzardi* infection has been reported.

Gentian violet by intravenous drip appeared to be moderately effective against *Mansonella ozzardi*, while totally ineffective against *Wuchereria bancrofti* in one case of mixed infection.

No serious toxic effects were observed from either of these drugs.

#### REFERENCES

1. BROWN, H. W.: Proc. Soc. Exper. Biol. & Med., **39**: 98, 1938.
2. KEIL, E.: Arch. f. Schiffs- u. Tropen-Hyg., **40**: 400, 1936.
3. MUCKERJEE, J.: Rev. de Méd. et d. Hyg. Trop., **28**: 37, 1936.
4. CHEU, S. H., KHAW, O. K.: Proc. Soc. Exper. Biol. & Med., **32**: 1394, 1935.
5. NEUBER, E.: Wien. klin. Wchnschr., **48**: 486, 1935.
6. SANTOS, C.: Rev. Radiol. e Clin., **3**: 875, 1934.
7. MACFIE, J. W.: J. Trop. Med., **23**: 36, 1926.
8. ASHFORD, B. K., SNYDER, H. M.: Puerto Rico J. Pub. Health & Trop. Med., **8**: 375, 1933.
9. U. S. Nav. M. Bull., **25**: 459, 1930.
10. DALAL, C. M.: Indian Med. Gaz., **62**: 449, 1927.
11. GIRAUD, G.: Thèse de la Faculté de Médecine de Paris, 1920.
12. LAURIE, E.: Lancet, **1**: 364, 1891.
13. ADLER, S.: Ann. Trop. Med. & Parasit., **17**: 427, 1923.
14. SIEBERT, H.: Arch. f. Schiffs- u. Tropen-Hyg., **24**: 334, 1924.
15. CHOPRA, R., AND RAO, J.: Ind. J. Med. Research, **27**: 549, 1939.
16. HAWKINS, F.: J. Trop. Med., **43**: 204, 1940.
17. KHAW, O. K., CHEU, S. H.: Chinese M. J. Supplement I, p. 402, 1936.
18. BROWN, H. W.: J. A. M. A., **125**: 952, 1944.
19. BROWN, H. W., SHELDON, A.: J. A. Vet. M. A., **98**: 477, 1941.
20. LAURIE, E., YORKE, W.: Ann. Trop. Med. & Parasit., **33**: 289, 1939.
21. DEVINE, J.: Ann. Trop. Med. & Parasit., **34**: 67, 1940.
22. NAPIER, L., GUPTA, P., AND SEN, G.: Indian Med. Gaz., **77**: 321, 1942.
23. KIRK, R., SATI, M.: Ann. Trop. Med. & Parasit., **34**: 83, 1940.
24. McLEITCH, J. L.: Ann. Trop. Med. & Parasit., **34**: 73, 1940.
25. LOW, G.: Brit. M. J., **1**: 196, 1920.
26. BREVI, H.: Medical Bulletin of the Standard Oil Co., **5**: 372, 1943.
27. FAUST, CARROLL: Human Helminthology, 1939. pp. 233, 400, 464.
28. HALL, C. H.: West Virginia M. J., **20**: 234, 1925.
29. MOOSER, H., AND MONROE, P.: Med. J. & Rec., **119**: 58, 1924.
30. VISHER, J. W.: J. Nerv. & Ment. Dis., **62**: 376, 1925.
31. BURKE, V., AND NEWTON, J. L.: J. A. M. A., **86**: 529, 1926.
32. CHURCHMAN, S., AND HERZ, L.: J. Exper. Med., **18**: 579, 1913.

## NON-SPECIFIC LOCALIZED GRANULOMATOUS ULCER OF THE JEJUNUM

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[From the Surgical Service of Dr. John H. Garlock]

Recently, a patient came under observation who presented symptoms of intermittent small bowel obstruction. Laparotomy with resection of a portion of the jejunum was performed for a lesion which pathologically proved to be a single non-specific primary ulcer. Because of its rarity, the case is described in detail.

### CASE REPORT

*History:* (Adm. #527058). The patient, a 61 year old married woman with three children, born in Austria, was first admitted to the hospital on August 13, 1944, complaining of vomiting, epigastric distress, and cramps of two months duration. Her past history was essentially negative, except for hypertension treated by diet. There were no previous operations. An upper gastro-intestinal series performed two days before admission was reported as negative. The referring physician's diagnosis was "an intestinal obstruction possibly due to a colonic neoplasm" because of cramp-like pains and visible peristalsis noted in the left abdomen. Temperature on admission was 100°F. The physical examination was essentially negative. Blood pressure was 150 systolic and 90 diastolic; hemoglobin, 79 per cent, white blood cell count, 13,900, with a normal differential. Urine was negative, bile, 0, urobilin, 1 to 5. The patient's symptoms disappeared promptly after admission. She became afebrile, and her request to leave the hospital was granted on the third day. She was readmitted on November 6, 1944, with complaints of recurrent attacks of abdominal pain, mainly in the left lower quadrant, associated with diarrhea, but no vomiting. The attacks occurred at intervals of about one week, and lasted three days. There was no icterus, hematemesis, or melena. A loss of 15 to 20 pounds in weight had occurred since the previous admission three months ago. Free acid had been found in the gastric contents, but no blood in the stools according to her family physician. Examination showed her to be apprehensive, and she showed obvious weight loss (present weight 93 pounds). There was a sense of resistance in the left half of the abdomen with evidence of visible peristalsis at times. When the cramps occurred, tenderness was present in the left upper quadrant. Under observation, the cramps would disappear, accompanied by borborygmi. The blood pressure was 138 systolic and 68 diastolic, hemoglobin, 65 per cent; red blood cell count, 3,930,000; white blood cell count, 8,100, with normal differential. The sedimentation rate was 20 mm. in one hour. Blood Wasserman was negative; urea nitrogen 13 mg. per cent; blood sugar 95 mg. per cent. Repeated stool examinations for blood were negative. Two barium enema examinations were negative. It was the opinion of the Surgical Service that the patient had an intermittent small bowel obstruction, probably due to a tumor. A small bowel x-ray series was requested, but the patient refused this examination.

*Operation:* (G.D.O.) On November 21, 1944, under ethylene ether anesthesia, an exploratory laparotomy was performed through a left upper mid-rectus incision. About 18 inches below the fossa of Treitz, there was a firm nodular mass involving the mesenteric side of the jejunum which, together with adjacent mesenteric lymph nodes, measured about 6 x 4 x 3 cms. This was adherent to the mesial anterior aspect of the mid-descending colon, and below it passed several loops of small bowel. The adhesions were divided. The jejunum above the lesion was dilated to about three times the size of the distal bowel, and its wall was thickened and edematous. No metastases were found; the uterus was somewhat enlarged and contained small fibroids. The presumptive diagnosis was a neoplasm of the

jejunum. The jejunum and a wedge of mesentery were resected between Payr clamps. Both ends were closed, and an isoperistaltic side to side jejuno-jejunostomy was performed. The patient made an uneventful convalescence, and was discharged from the hospital on the twelfth post operative day. When seen two months later, she was well and asymptomatic.

*Pathological examination:* The appearance of the lesion when the resected intestine was first opened, suggested an ulcerated lymphosarcoma or myosarcoma. The following is the description and diagnosis from the Department of Pathology.

"Specimen #86849: Loop of jejunum measuring 23 cm. In its middle is a circular area 3.5 cm. in width where the lumen is strikingly stenosed. The opened proximal portion is markedly dilated, measuring 10 cm. in width, in comparison with the distal portion which measures 3.5 cm. The serosa opposite the area of stricture is puckered, thickened, and injected. This was the site of the divided adhesions to mid-descending colon. The fat tissue of mesentery is firmly adherent. Area of constriction shows a deep ulceration. The edges of the ulceration are indurated and elevated, the base of the ulceration formed by necrotic tissue which bulges over the surface. On the serosal surface, one can see some grayish infiltration in a net-like arrangement. The lymph nodes are firm, enlarged, and fibrous. The mesentery opposite the stricture is fibrous and firmly attached to the wall. The mucosa of the remainder of the jejunum is smooth, freely moveable, and pale."

*Microscopic description:* (Dr. S. Otani). "Circumscribed, ulcerated chronic and acute, non-specific jejunitis with marked cicatrization and stricture. No evidence of tumor or foreign bodies found."

*Subsequent Clinical Course:* The patient was apparently well for the next six months. She then reentered the hospital with complaints of jejunal obstruction, and a second operation disclosed a local recurrence of the previously removed lesion. The surgical material is still under investigation and presents problems which when solved will be reported at some later date in this Journal under the heading of "recurrent localized granulomatous ulcer of the jejunum."

#### DISCUSSION

The clinical picture above described may be considered rather typical of a partially obstructing lesion of the jejunum. In the absence of post operative adhesions causing obstruction, the most common cause for jejunal obstruction is a benign or malignant neoplasm. Although uncommon, we have seen several such jejunal tumors. One was a lymphosarcoma, and one was a myosarcoma. High obstruction due to herniation at the fossa of Treitz or from extrinsic neoplasm invading the bowel have been reported. Although carefully performed on several occasions, no blood was found in the stool by guaiac tests. In the presence of an ulcer, one might expect to find occult blood, although typical gastric or duodenal ulcers do not show a positive guaiac in the stool unless there is actual bleeding. The exact location of the lesion would have been demonstrable with a small bowel series performed with a Levine or Miller-Abbot tube if the patient had permitted radiography for this purpose.

Non-specific ulcer of the jejunum is apparently a very rare lesion. According to Robinson and Wise (1), only 59 cases of a similar sort have been collected in the literature up to 1940, and of these, 46 were in the ileum, and only 13 were in the jejunum. Incidentally, a great number of these lesions were found, at operation or on post-mortem examination, to be perforated. Combes, in 1897, Leotta, in 1919, Richardson (2), in 1922, Ravdin (3), in 1927, and Buckstein (4), in 1939, reported and reviewed similar cases. In attempting to ascertain the



etiology of the above described single ulcer of the jejunum, a careful search for neoplasm was made; then, the possibility of foreign body granuloma with ulceration was entertained. Examination of many sections showed no signs of any foreign body. Evidences of specific cause of usually multiple ulcerations in the bowel, such as typhoid, dysentery, tuberculosis, syphilis, etc., were not found. Some authors (1) on the basis of the occasional finding of aberrant gastric mucosa in the jejunum and ileum not associated with a Meckel's diverticulum, have explained such non-specific ulceration on the basis of heterotopic gastric mucosa. Histologic evidence of gastric mucosa in a Meckel's diverticulum with ulceration is not uncommon. However, there was no gastric mucosa in the resected specimen.

Multiple ulcerations of the jejunum have been seen as part of the diffuse, non-specific lesion called jejuno-ileitis which may be related to regional ileitis, a subgroup of the intestinal granulomata described in 1932 (5, 6). We have seen multiple jejunal and ileal ulcerations in a few instances of diarrheal disease characterized pathologically by a peculiar hyperplasia of the lymphoid tissue of the small bowel and the mesenteric lymph nodes. When studying the group of non-specific granulomata of the bowel (5, 6), we observed but excluded two cases of localized ulcerative jejunitis which we were unable to classify. Vascular changes such as endarteritis and thrombosis could, when present, explain a small bowel ulceration. In the absence, then, of any discernable, specific cause, and in the presence of an ulcer with a surrounding inflammatory process causing obstruction, the lesion may be best described as a non-specific granulomatous ulcer of the jejunum.

#### BIBLIOGRAPHY

1. ROBINSON, D. R., AND WISE, W. D.: Simple Non-Specific Ulcer of the Jejuno-Ileum. *Surg., Gynec., & Obst.*, 70: 1097, 1940.
2. RICHARDSON, E. P.: Jejunal Ulcer Without Previous Gastro-Enterostomy. *Surg., Gynec., & Obst.*, 35: 1, 1922.
3. RAVDIN, I. S.: Primary Ulcer of the Jejunum. *Ann. Surg.*, 75: 873, 1927.
4. BUCKSTEIN, J.: Primary Ulcer of the Jejunum. *Radiology*, 33: 299, 1939.
5. GINZBURG, L., AND OPPENHEIMER, G. D.: Non-Specific Granulomata of the Intestine. *Ann. Surg.*, 98: 1046, 1933.
6. ———: Non-Specific Granulomata of the Bowel. (Inflammatory Tumors and Strictures.) *Tr. Am. Gastro-Enterol. Soc.*, May, 1932.

## CHRONIC EMPYEMA ASSOCIATED WITH OSTEOMYELITIS OF SPINE AND RIBS\*

A. H. AUFSES, M.D.

*Case 1. History.* The patient is a man of 38, who was admitted to the hospital three weeks ago. Eight years previously he had a cold, was given a mustard plaster, and boils developed on his back. One boil was incised in the doctor's office, but he developed others and had to be taken to the hospital. He remained there four and a half months, during which time he had a thoracotomy and rib resection. He recovered and was well until about three years ago when one of the old scars opened and sinuses formed. The sinuses have drained intermittently until the time of admission. In the course of the past two years he had episodes of chills and fever. He reentered the hospital with a temperature of 103°F.

*Course.* A plate taken before admission showed the previous rib resection and an elliptical paravertebral shadow. Lipiodol was injected into the sinus, and a second film (fig. 1) showed that the lipiodol ran to or near to the vertebral bodies. At operation, the sinus was split open, and the eighth rib was removed because the sinus was found to run beneath it. The eighth rib was followed back to the vertebral body, which disclosed a small abscess cavity beneath the posterior end of the rib.

It was not certain at operation whether the entire lesion had been unroofed but there was nothing at this time to suggest any other sinuses or collections of pus.

Following operation, another lipiodol injection was made. An x-ray taken prior to the injection showed a small blotch of lipiodol, apparently left from the original injection, situated a considerable distance away from the sinus tract discovered at operation.

The patient was again operated upon, and the ninth, tenth, and eleventh ribs removed; another abscess was found in this area close to the bodies of the vertebrae. Culture of the pus revealed a beta-hemolytic *Streptococcus*. One x-ray showed a suggestion of osteomyelitis of a vertebral body, and this raised the question of interpretation of the elliptical paravertebral shadow seen previously. A diagnosis of paravertebral abscess was suggested.

*Comment.* This patient, as far as it is known had an empyema drained eight years ago, following which he was apparently well. It is questionable, however, whether he had a true empyema at that time or an osteomyelitis of the vertebrae metastatic from the boils which he had had on his back. We raise this question because we have had a number of other patients in whom osteomyelitis of the vertebra was unsuspected for many years, the disease manifesting itself as chronic empyema which failed to heal or became recurrent.

The next case is much more conclusive in that we have a very good insight into the early history.

*Case 2. History.* This patient is now 25 years of age. A presumed empyema was drained in another hospital ten years ago. Following this procedure, it was observed on some of the films that he had osteomyelitis of a vertebra. Going back into his history, they then found that his illness began with rigidity of the neck and pain in the back, and he also had a history of a "boil infection." *Staphylococcus aureus* was cultured from the drainage pus.

Following a three year period of comparative freedom from symptoms a sinus opened and began to drain pus. It was at this time that he came under our care.

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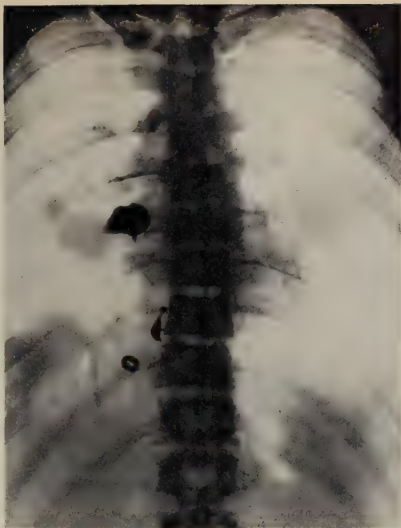


FIG. 1. Lipiodol injected into chest wall sinus appears in the region of the vertebra<sup>1</sup> bodies.

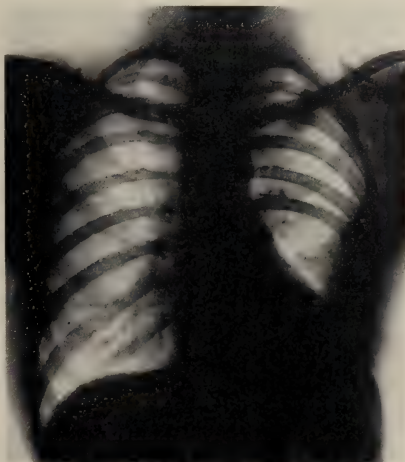


FIG. 2. A collection of fluid at the base of the left pleural cavity is shown.

He was operated upon, and a large collection of pus was evacuated; a tract was found extending back toward the vertebral column. Unfortunately, his condition became poor on the operating table and the operation had to be discontinued.

Following the operation, his wound healed well and for that reason this tract was not investigated further.

Two years later, he was readmitted with a small sinus which was opened and a piece of osteomyelitic rib removed. There was a persistent shadow in the axillary area (fig. 2). At this time he complained of pain in the back radiating to the front of the chest, and received several alcohol injections of the intercostal nerves for relief of this pain.

An x-ray in 1942 revealed that the axillary shadow had increased slightly, but he was otherwise well for the next three years when he began to complain of fatigue and slight fever.

In May, 1944, he was readmitted, and x-rays showed a further increase in the axillary shadow. This had always been visible and one might, in the early stages, have said that this was indicative of "thickened pleura." We have found it inadvisable to call such shadows thickened pleura, because they often are discovered to be chronic empyema. Aspiration revealed thick pus, and a large cavity was partially unroofed.

Penicillin mold on gauze was packed into the wound and the infection cleared up very quickly. Although we felt that sufficient surgery had not been performed (only part of the cavity had been unroofed), we decided to give the penicillin a chance to sterilize the cavity. His wound healed, and he left the hospital in October, 1944.

The wound opened again, drainage occurred, and he still had a shadow on the film. At operation, the empyema cavity was reopened, and it was found that the part that had not been opened previously was still present. The remainder of the empyema cavity was completely unroofed surgically, and when he left the hospital the boy had a clean granulating wound, with the soft tissues filling in the dead space. That was only a couple of weeks ago.

*Comment.* Here, then, is a case of osteomyelitis of the vertebra which has run a long course. We have found that in all of them a correct diagnosis was reached only after a long time. They require frequent operations, and in this case we have the additional evidence that although penicillin may be a good adjuvant to surgery, it cannot take the place of good surgery; therefore, where surgery is indicated, it should be performed.

## THE MILIARY FORM OF PULMONARY SARCOIDOSIS\*

SOLON S. BERNSTEIN, M.D.

Pulmonary lesions are very common in sarcoidosis, appearing at some phase in the evolution of the disease in about 90 per cent of the reported cases. The lungs rank second only to the lymphatic structures in frequency of involvement. Moreover, sarcoidosis limited to the hilar and peribronchial nodes without pulmonary dissemination is one of the most frequent forms of the disease. This discussion will be concerned largely with the intrinsic pulmonary infiltrations, of which the miliary and submiliary types are particularly arresting because they are often roentgenographically indistinguishable from miliary tuberculosis.

The bulk of the intrinsic pulmonary lesions may be grouped into: A. the linear strand-like pattern, extending from the hilar zone to the periphery, often along the medial portions of the lower lobes; hilar adenopathy is frequently present. The diffuse streaking is presumably due to the predilection of sarcoid tissue for the lymphatic structures in the interlobar septa; B. diffuse confluent densities of a patchy character, often combined with linear infiltration; and C. miliary and submiliary forms, consisting of diffusely disseminated small nodular foci, often simulating miliary or hematogenous tuberculosis. Although usually distributed widely throughout both pulmonary fields, miliary infiltrations are at times limited to the mid-pulmonary and basal areas. Transitions from one type of infiltration to another have been frequently noted under prolonged observation and all combinations are found (1). In sarcoidosis the chest roentgenogram gives little information as to the severity of the disease, since a paucity of symptoms and signs may accompany massive infiltrations. On the other hand, serious disability may ensue due to invasion of other structures, with either minimal or absent pulmonary involvement.

The diagnosis of sarcoidosis cannot be accurately established merely by the presence of miliary or submiliary x-ray shadows. In a comprehensive review, Rabin (2) designates nodular shadows as *miliary* if they do not exceed 1 mm. in diameter, and *submiliary* if they are from 1 to 3 mm. in diameter. He mentions miliary tuberculosis, miliary carcinosis, asbestosis and hyphomycetosis as indistinguishable from the miliary form of sarcoidosis. The submiliary shadows, which are found with even greater frequency in sarcoidosis, cannot be differentiated, on the basis of roentgen evidence alone, from the following diseases: hematogenous tuberculosis (tuberculous bacillosis), metastatic carcinosis, submiliary pneumonia, bronchiolitis, bronchiolitis obliterans silicosis and pulmonary congestion. The diagnosis of sarcoidosis cannot therefore be made on roentgen evidence alone, but must rest on the confirmatory evidence of a positive biopsy, either cutaneous or lymphatic.

Reisner (3), in a study of the pulmonary lesions in sarcoidosis, believes that the miliary-like dissemination represents the earliest invasion stage of the

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disease. This is in accord with our experience that the cases with the shortest duration of symptoms tend to have a miliary distribution. Further, as previously described, the tendency to spontaneous regression of the miliary and submiliary shadows is to be distinguished from the irreversibility of the lesions in the conglomerate and linear types, where fibrotic changes are more prone to occur. Although fibrosis is very difficult to demonstrate roentgenologically, Klemperer (4) points out that hyalinization and fibrosis have been found at autopsy in sarcoid tissue. King (5), however, in a series of 39 cases, found complete resolution of the pulmonary lesions in from seven weeks to three years with an average of 22 months. In a small number of cases transition to a tuberculous infiltration with cavitation and, rarely, calcification, has been observed. This would tend to strengthen the position of those observers who feel that sarcoidosis is an attenuated or "anergic" form of tuberculosis.

Although specific therapeutic measures have been generally deemed ineffective in sarcoidosis, some observers have had encouraging results with roentgen therapy (6, 7). Pohle and his associates (8) have recently reported striking improvement with radiation therapy in eight out of fourteen cases of pulmonary sarcoidosis.

#### CASE REPORTS

*Case 1. History.* H. G., (Adm. #528494), a 21 year old colored woman, was admitted to The Mount Sinai Hospital on September 12, 1944 complaining of cough, persistent low grade fever and a skin eruption of seven months' duration. She had been well until the onset of her illness, when she noted anorexia, malaise and a skin eruption limited to the arms. This was soon followed by ptosis of the right upper lid, weakness of the right side of the face and some difficulty in swallowing; these latter symptoms persisted for several days. The cutaneous lesions gradually spread to involve the entire body, sparing only the palms and soles. The cough had been productive of a cupful of mucoid sputum daily. Wheezing respiration had been intermittently present.

*Examination.* The patient was a well-nourished young colored woman who did not appear ill. Her temperature on admission was 101.2°F., the pulse 100. There was a diffuse papulonodular cutaneous eruption consisting of discrete and confluent split-pea to small pea-sized lesions. They were widely distributed over the upper eyelids, right inner canthus and face. The posterior nuchal and supraclavicular regions were profusely covered. The eruption then spread to the entire back, anterior chest and arms. Distributed throughout the mouth, but chiefly in the hard palate, were a number of confluent, hard papules without an erythematous border. Adenopathy was generalized, with discrete firm nodes varying from 0.5 to 2 cm. in size. Scattered moist rales, slight dullness and diminished breath sounds were present over the right lower lung field.

*Laboratory.* The leucocytes numbered 5,200, with 31 per cent lymphocytes. There was polychromia of the red blood cells. The sedimentation time was 49 minutes (Normal: over one hour). The tuberculin patch test was negative. Repeated sputum examinations were negative for tubercle bacilli and guinea pig inoculations failed to induce tuberculosis. A Mantoux test was negative up to a dilution of 1:100. Biopsy of a cutaneous nodule and of a supraclavicular lymph node both revealed sarcoidosis. The chest roentgenogram (fig. 1) showed both lungs to be diffusely studded with small irregular submiliary nodules. The mediastinal lymph nodes appeared to be enlarged. There was a fine layer of exudate over the pleura on the right side. Both leaves of the diaphragm were displaced downward. It was deemed impossible to differentiate between a disseminated tuberculosis (miliary or submiliary) and sarcoidosis.

*Course.* She was almost completely asymptomatic throughout her hospital stay, but



FIG. 1. Case 1. Miliary sarcoidosis with enlargement of mediastinal lymph nodes

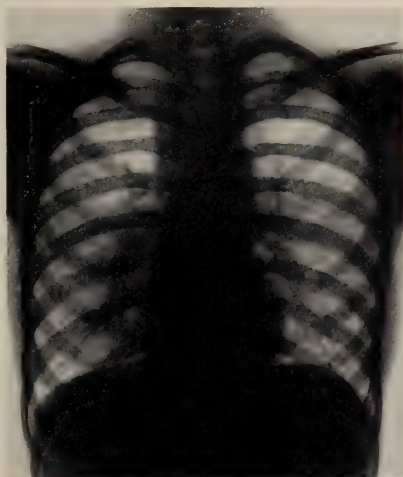


FIG. 2. Case 2. Miliary sarcoidosis

the persistent low grade fever indicated activity of the process. Subsequent chest films showed no change. She was last seen on March 26, 1945, when cough and expectoration were minimal and the temperature was normal; she had gained weight and was quite comfortable, although not working.

*Summary.* A 21 year old negress with a seven month history of cough, expectoration and fever, presented a diffuse cutaneous eruption and generalized adenopathy. Biopsy of both skin and lymphatic tissue disclosed sarcoidosis. The chest x-ray revealed diffuse infiltration with submiliary nodules which could not be distinguished from disseminated miliary tuberculosis. The duration of the disease and ultimate outcome are unpredictable.

*Case 2. History.* H. H., (Adm. #536069), a 15 year old Porto Rican male who had been deaf since an accident at the age of two, was admitted to The Mount Sinai Hospital on August 30, 1944 with a one month history of intermittent pain in the right costovertebral area, frequent vomiting with some nausea, and a loss of twelve pounds in weight.

*Examination.* He appeared thin and chronically ill. There was a pea-sized adenopathy in the cervical, epitrochlear and inguinal regions. The chest showed slight increase in the area of retromanubrial dullness and some scattered areas of diminished breath sounds posteriorly. A generalized macular rash with some scarring and pigmentation was diffusely distributed over the trunk and extremities. A firm spleen descended 3 cm. below the costal margin. The right kidney appeared enlarged and was freely ballotable.

*Laboratory.* The leucocytes numbered 5,200, with a normal differential. The urine contained a faint trace of albumin with some granular casts. The blood Wassermann was negative. The Mantoux test was negative in a dilution of 1:100. No tubercle bacilli were found in repeated sputum examinations, and guinea pig inoculations were negative. Biopsy of a cervical lymph node disclosed sarcoidosis. A section of the skin proved the skin papules to be a juvenile verruca plana. X-ray of the chest (fig. 2.) revealed extensive submiliary infiltrations in both lungs, more pronounced at the bases; the hilar nodes were slightly enlarged.

*Course.* He had occasional low grade fever, but was for the most part afebrile. He experienced several episodes of vertigo, accompanied by nausea and vomiting. With the aid of sedation and intravenous glucose and saline, a prolonged attack was controlled. Spinal fluid and renal studies were negative.

*Summary.* A 15 year old Porto Rican boy had fever and costovertebral pain for one month. There was diffuse adenopathy, and biopsy of a node disclosed sarcoidosis. Diffuse bilateral submiliary infiltrations were found in the chest roentgenogram. Relevant symptoms were minimal and the roentgen picture did not change during several months of observation.

#### COMMENT

The striking resemblance between the pulmonary roentgenogram of miliary sarcoidosis and miliary tuberculosis is exemplified by two instances of sarcoidosis. Although the two diseases are often roentgenographically indistinguishable, the diagnosis can, as a rule, be established both by the clinical course and by laboratory evidence. The indolent, and at times symptomless, character of sarcoidosis despite wide extension, is to be contrasted with the clinical severity and accelerated tempo of miliary tuberculosis. A definitive diagnosis of sarcoidosis rests solely on cutaneous or lymphatic biopsy evidence. In the presence of extensive miliary or submiliary pulmonary infiltration, with negative or minimal physical signs, a mild subfebrile course, negative sputum and guinea pig inoculations, and a negative tuberculin response, the possibility of sarcoidosis should be seriously considered. There is considerable evidence that miliary sarcoidosis represents the early or invasive stage of the disease. Complete reversibility with disappearance of the pulmonary shadows has been repeatedly observed.

## REFERENCES

1. BERNSTEIN, S. S., AND SUSSMAN, M.: Thoracic Manifestations of Sarcoidosis. *Radiology*, 44: 37, 1945.
2. RABIN, C. B.: Radiology of the Chest, in *Diagnostic Roentgenology*. New York, T. Nelson and Sons, 1941, p. 1918.
3. REISNER, D.: Boeck's Sarcoid and Systemic Sarcoidosis. *Am. Rev. Tuberc.*, 49: 289, 437, 1944.
4. KLEMPERER, P.: Personal Communication.
5. KING, D. S.: Sarcoid Disease as Revealed in the Chest Roentgenogram. *Am. J. Roentgenol. and Rad. Ther.*, 45: 505, 1941.
6. BERNSTEIN, S. S., AND OPPENHEIMER, B. S.: Boeck's Sarcoid. *J. Mt. Sinai Hosp.*, 9: 329, 1942.
7. KATZ, S., CAKE, C. P., AND REED, H. R.: Sarcoidosis. *New England J. Med.*, 229: 498, 1943.
8. POHLE, E. A., PAUL, L. W., AND CLARK, E. A.: Roentgen Therapy of Boeck's Sarcoid. *Am. J. Med. Sci.*, 209: 503, 1945.

# STAPHYLOCOCCUS AUREUS EMPYEMA IN AN INFANT, AGED SIX WEEKS. STREPTOCOCCUS VIRIDANS EMPYEMA IN AN INFANT, AGED TWENTY-ONE MONTHS\*

E. E. ARNHEIM, M.D.

The problems of suppurative pleuritis in infants and children differ from those in adults. The cases to be presented illustrate two types of suppurative pleuritis in infancy; in one case due to a *Staphylococcus aureus* infection; in the other, the pleural infection was caused by *Streptococcus viridans*.

Neuhof and Hirshfeld (1) drew attention to this subject in 1932, and there have been relatively few contributions since that publication. The great problem in all of these cases of suppurative pleuritis in infants has been the very high mortality, particularly in staphylococcus aureus pleuritis. For example, in a paper by Neuhof and Berek (2), in 1935, the mortality rate of staphylococcus aureus empyema in infants was 52.5 per cent, and in a paper by Ladd and Swan (3), in 1943, the mortality rate was 66.7 per cent. These cases antedated the use of penicillin, and in many the use of sulfonamides.

## CASE RECORDS

*Case 1. History.* R. K., (Adm. 526476), a female infant, aged six weeks, was admitted to the hospital on October 21, 1944. At the age of three weeks, the child had a very small abscess in the region of the right breast. This apparently was superficial, because the mother stated it healed in a period of two days after drainage of pus. The child was then well for three weeks. Two days before admission to the hospital she began to have fever, was dyspneic, and coughed. The fever ranged between 102°F. and 103°F.

*Examination.* The temperature was 103°F., and respiration very rapid, somewhere around 100 per minute. The child was dyspneic, quite cyanotic, and obviously suffering from real respiratory distress. There was dullness to flatness over the right side of the chest.

*Laboratory Data.* Blood: hemoglobin, 55 per cent; leucocytes, 19,800, of which 33 per cent were polymorphonuclears. X-ray examination of the chest (fig. 1) showed a homogeneous density on the right side which was interpreted as a large collection of fluid in the pleural cavity. There was slight displacement of the heart to the left, but there was some rotation of the position of the patient.

The chest was aspirated on the right side posteriorly, and some thin purulent fluid obtained. During the next few hours, the patient presented the picture of increasing respiratory difficulty.

*Operation.* Under local anesthesia, closed drainage was performed on the day of admission. A catheter connected to an underwater drainage system was inserted in the eighth intercostal space posteriorly. Thin, purulent fluid and a little air was evacuated. Cultures of the fluid obtained both on aspiration and at operation showed *Staphylococcus aureus*, which was found to be two and one-half times as resistant to penicillin as the standard organism.

*Course.* 136,000 units of penicillin were administered intramuscularly during the first three postoperative days. X-ray of the chest on the fourth postoperative day (fig. 2) revealed considerable clearing of the density, indicating that most of the fluid had been drained.

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FIG. 1. Large effusion in the right chest with some shift of the cardiac shadow to the left

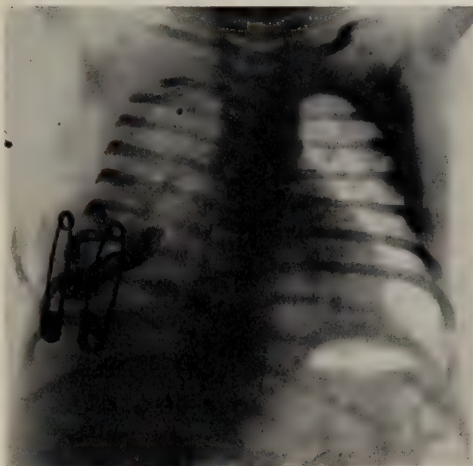


FIG. 2. Most of the fluid has been drained from the right pleural cavity, drainage tube in pleura

The child improved clinically, and the closed drainage was discontinued on the fourth postoperative day. The tube was cut, allowing it to drain into the dressings instead of under water. A whole blood transfusion was given and on the third postoperative day the child was taken out of the oxygen cubicle. The temperature remained elevated to 102°F. for six days, and because of the fever, 144,000 units of penicillin were given in the course of the next three days. Nine days after operation the temperature was normal; and a roentgenogram on the twelfth day showed further clearing of the pleuritis. There was some residual pleuritis around the drainage site. The tube remained in place, draining a small amount of thin purulent fluid.

*Comment.* The future course is difficult to predict at this time; it is not certain whether or not this child will require a rib resection for more adequate drainage

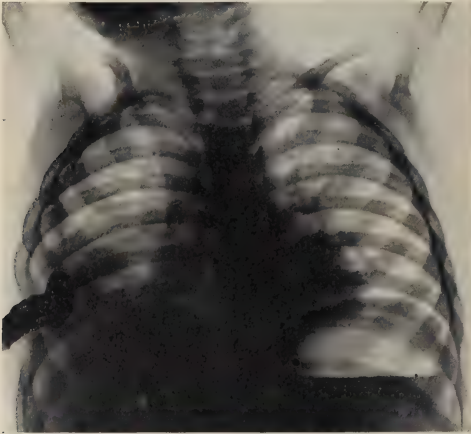


FIG. 3. 15 days post operative.—Almost all the fluid has been drained from the right pleural cavity. Iodoform packing in wound.

in fact, there is a good possibility that the infant will be cured by simple closed drainage. One of the questions to be considered is the pathogenesis of the infection. The history of an abscess three weeks before (which was not cultured, but which in the vast majority of cases is due to a *Staphylococcus*) is presumptive evidence that metastasis from the skin infection resulted in lung abscesses with extension to the pleura. The question arises as to whether these infants can be treated by Potain aspiration, which is a common and accepted mode of treatment of pleuritis. We believe that the fluid reaccumulates after such aspiration, and the adhesions which form make later surgery more difficult. The satisfactory results obtained by simple, closed drainage warrant the use of this procedure, which may be supplemented later by rib resection, if necessary. The mortality has been due, in part, to the fact that these children had multiple lung abscesses.

With the advent of penicillin, it is hoped that in conjunction with prompt surgery its use will lead to a definite reduction in mortality. Experience with penicillin in the treatment of staphylococcus aureus empyema in infancy is limited but the prompt, satisfactory course of recovery in this infant indicates that penicillin was a significant factor.

*Case 2. History.* S. B. (Adm. 526075), a male infant, aged 21 months, was admitted to the hospital on October 11, 1944. The infant had aspirated an Indian nut about two months before admission, and the next day or two seemed weak and tired. The nut was removed by bronchoscopy and the child was hospitalized for the next week.

X-ray of the chest after the Indian nut was aspirated, prior to bronchoscopy, showed an area of infiltration in the right lung.

Following bronchoscopy a pneumothorax developed but he was apparently well for a period of six weeks. Two weeks before admission he developed fever and dyspnea. A roentgenogram of the chest at this time showed a diffuse shadow in the right lung field.

*Examination.* The child was acutely ill, with a temperature of 104.6°F., and rapid pulse and respirations. There were physical signs of fluid in the right chest.

*Operation.* (Dr. Neuhof) On the day of admission, posterior segments of the sixth and seventh ribs were excised. Multiple, encapsulated pockets of pus in the right pleural cavity were drained and packed. Culture of the pus grew out *Streptococcus viridans*.

*Course.* During the first postoperative week there was a daily temperature elevation to 101°F. It fell slowly, becoming normal on the sixteenth postoperative day. X-ray of the chest fifteen days after operation (fig. 3) showed the iodoform packing at the site of the drainage, there was considerable clearing of the collection of fluid, and some pleural exudate along the right lung toward the apex. The lung was partly collapsed, but there were small areas of rarefaction within it.

*Comment.* This child was treated quite differently from the infant with *Staph. aureus* empyema because he was seen later in the course of the disease than the first patient. The acute episode lasted at least two weeks, and the infection had been present some time before that. It was safe, therefore, in this case to perform an immediate rib resection. The chronicity of the infection was demonstrated by the loculation of pus in the pleural cavity.

The incidence of *Strep. viridans* empyema in infancy is low. Neuhof and Hirshfeld (1) recorded seven cases, of which one died, a mortality of 14 per cent.

#### REFERENCES

1. NEUHOF, H., AND HIRSHFELD S.: Suppurative Pleuritis in Children. *Am. J. Dis. Child.*, 44: 973, 1932.
2. NEUHOF, H., AND BERCK, M.: Staphylococcic Empyema and Pyopneumothorax. *Arch. Surg.*, 30: 543, 1935.
3. LADD, W. E., AND SWAN, H.: Mortality in Acute Staphylococcal Empyema in Infants and Children. *J. Pediat.*, 23: 297, 1943.

# ESSAYS ON THE BIOLOGY OF DISEASE<sup>1</sup>

ELI MOSCHCOWITZ, M.D.

## CHAPTER 12

### PERIARTERITIS NODOSA

Periarteritis nodosa is a morphological entity, and possesses only a minor clinical significance. The essential lesion is a fibrinoid necrosis of the media, with swelling of the wall, destruction of the elastic laminae and a perivascular infiltration with cells, which may be polymorphonuclear, sometimes eosinophilic, and histiocytes or both. There may be proliferation of the intima in the later phases. The destruction of the vascular wall often leads to aneurysm formation, leading to the formation of nodes in the course of the vessels. In early lesions this is not seen. Klemperer (1) believes that in the absence of aneurysm, the term "necrotizing arteritis" is more applicable. This however does not necessarily imply that it is a different lesion. The fact that both types of lesions are usually found simultaneously and that the aneurysm is often only of microscopic dimensions is an indication that the aneurysm represents a later stage, induced by prolonged intravascular pressure, either normal, or, as so frequently occurs in periarteritis nodosa, increased. As a rule the lesions are diffuse; in exceptional instances, the lesions may be localized (2, 3). The classical lesions are seen mainly in vessels that are just visible to the naked eye although microscopically the smaller arteries and the vasa vasorum of the larger arteries are affected. Whether the capillaries are affected has not been determined. The lesions reveal a progression from an early active stage to healing with scar formation. Fishberg (2) described what is probably the earliest phase in an individual whose clinical history began only 6 days before death. The lesion was characterized by a deposition of fibrin in the walls; the intima was thickened by endothelial hyperplasia and hyalin and the walls of the arteries, both media and intima were infiltrated with polymorphonuclear leucocytes and occasional eosinophile cells. It is significant that the characteristic infiltration of the adventitia was absent. There were no aneurysms. In other words, the lesions presented all the ear marks of an exudative inflammation, and whether the lesion proceeded from within outwards or reversely was not clear. Arkin (4) described four stages: 1. an alterative degenerative; 2. an acute inflammatory; 3. granulation; 4. scar tissue. The report of Baehr and Manges (5) is noteworthy because two stages, four months apart, could be studied. The first

<sup>1</sup> This is the twelfth chapter in a series of essays by Dr. Eli Moschcowitz, in which an attempt will be made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. When the publication of the projected series of essays is completed, the several installments will be assembled and printed as a monograph.—Ed.

revealed an acute or subacute lesion, while the second showed extensive fibrillar degeneration of the internal elastic lamina, fibrous replacement of the media and a compensatory thickening of the intima. Keegan's (6) observation is somewhat similar; the right kidney was removed for a supposed surgical kidney; the renal vessel showed the acute lesion of periarteritis nodosa with necrosis and perivascular infiltration with polymorphonuclear cells, monocytes and occasional eosinophiles. Three months later, the patient died from renal insufficiency without hypertension. The renal vessels of the remaining kidney showed healing changes characterized by fibrosis of the walls, a marked fibrous intimal thickening, organized and canalized thrombi and a strictly mononuclear perivascular infiltration.

Jager (7) reports three cases of periarteritis nodosa with long clinical histories; one of 37 months, in which healed lesions were present characterized by extensive intimal scars, some of which were atheromatous. One obtains the distinct impression that the cellular infiltration changes from a preponderant polymorphonuclear in the early stage to an exclusive round cell type in the intermediate. The final phase represents a maturation of these elements with fibrosis, hyalinization, intimal thickening, and either narrowing of the lumen or aneurismal formation which may be either microscopic or macroscopic. Frequently, the lesions are associated with thrombosis which organizes and sometimes undergoes recanalization. In view of the destructive nature of the lesion one would not expect a complete anatomical restoration to normal.

However, such cicatricial or anatomical healing does not necessarily imply clinical healing. Arkin's patient died four years later from cardiac and renal failure. Jager's patient also revealed the clinical evidence of a juvenile arteriosclerosis. Spiro's (8) patient revealed aneurismal formation, cicatricial healing, and healed infarcts in various organs, but death occurred from hemorrhage arising from multiple intestinal ulcers, due to infarct formation. On the other hand, there are a number of reports of apparent clinical recovery, although in none was the period of observation over four years. [Carling-Braxton-Hicks (9), (2 years)], [Harris, Lynch and O'Hare (10), (4 years)], [Grant (11), (3 cases, three years, three years and one year respectively)]. Spiegel (12) quotes a number of apparently healed cases, reported previously to those we have just quoted. Plaut (13) and others (12) describe typical lesions in the diseased and even in the normally appearing appendix, and occasionally in the female generative organs removed at operations for suspected disease. Klemperer (68) holds that a considerable number of such cases are not genuine instances of periarteritis nodosa because the vascular lesion is not a necrotizing one, but represents a hyaline or fibrinoid change. This may account for the fact that so many of such patients recover completely. Whether they will remain so time alone will decide. I recall a case later reported by Gross and Friedberg (14) in which death occurred months after the pathological diagnosis had been made from a removed appendix. Indeed the ultimate fate of the few apparently healed clinical cases would be most instructive.



The disease occurs predominantly in males and has been found in mammals [Joest and Harzer (15)].

*Etiology.* In recent years there has been a strong trend to view periarteritis nodosa as an allergic tissue reaction. This was first suggested by Gruber (16) in 1925 on two clinical grounds; first, the occasional history of previous allergic manifestations such as asthma (12, 17, 18, 11); and second, the very common history of a prodromal infection [Spiegel (12)]. Experimental verification of this suggestion has since arisen. Metz (19) in 1931 produced lesions identical to those of periarteritis nodosa by sensitization of animals with foreign serum and the streptococcus. Gerber (20) by means of repeated intravenously administered bacterial filtrates produced among other changes a necrotizing arteritis limited to the kidney with perivascular leucocytic infiltrative lesions which he believed represented a Schwartzman phenomenon. Masugi and Osibasi (21) obtained diffusely distributed lesions of periarteritis nodosa by sensitization with various bacterial strains. The anaphylactic nature of human periarteritis nodosa was first brought prominently into focus by Clark and Kaplan (22) who reported two cases of pneumococcus serum sickness in which typical lesions were found at autopsy. Later, Rich (23) reported periarteritis nodosa in five patients with serum sickness, and in one that received sulfathiazole alone. In one patient who recovered from the attack of serum sickness, hypertension and a slight diminution in renal function developed three months later. Subsequently Rich and Gregory (24) produced lesions in rabbits identical to those of periarteritis nodosa by sensitization with foreign serum. They regard these lesions as exaggerated expressions of the Arthus phenomenon, the histological structure of which was fully described by Gerlach (25) in 1923, who showed that in this phenomenon there is localized vascular necrosis with perivascular infiltration. Whether sulfathiazole produces the reaction directly or by way of sensitization will be later investigated by Rich and Gregory.

Rich and Gregory found these lesions fully developed after the seventh day of sensitization, thus confirming Fishberg's findings in his earliest reported human case. On the basis of their findings, they deem it important to determine and if possible to neutralize the responsible antibody in cases diagnosed during life.

These observations which seem highly convincing are significant not only because they are in accord with the clinical observations mentioned previously, but also because of the common coexistence of periarteritis nodosa with certain basic maladies whose genesis has also been ascribed to sensitization, namely, rheumatic fever and glomerulonephritis.

a. Rheumatic fever and periarteritis nodosa. There are a considerable number of reports of the association of periarteritis nodosa with rheumatic fever. The vast majority are invalid for purposes of proof, because the diagnosis is based on clinical data alone. In order to be decisive, it is essential to establish not only a clinical history of rheumatic fever but the characteristic rheumatic endocarditis and the presence of Aschoff bodies. With these criteria in mind, the report of Friedberg and Gross (14) is conclusive. Of a total of eight instances of periarteritis nodosa observed in the course of two years, they report

four in which these criteria were fulfilled. In addition to these four cases, Friedberg and Gross report two that ran a febrile course with arthritis and clinical evidences of glomerulonephritis and in whom at autopsy verrucous endocarditis but without Aschoff bodies were found. In view of this considerable percentage (50 per cent), the probability is strong that rheumatic fever and periarteritis nodosa are common associations. With less rigid criteria the number of reported cases of the association would be greater. One must remember that a larger number of reports antedated the discovery of the Aschoff body as the specific lesion of rheumatic fever, and furthermore, that no search for these bodies was made, or (what is more likely) the search was insufficient, because it sometimes requires a painstaking effort.

In a later report, Gross, Kugel and Epstein (3) report a necrotizing arteritis identical to that of periarteritis nodosa in the coronary vessels in 11 of 66 hearts affected by rheumatic fever. Four of these are included in their previous report, because the lesions were present throughout the vascular system. In the remaining seven the lesions were strictly limited to the coronary vessel. Whether periarteritis nodosa should be differentiated from "necrotizing arteritis" merely on the criterion of the local or generalized distribution is very doubtful. Klinger and Vaubel (26) in reporting the autopsy findings on their cases of rheumatic fever could not differentiate many of the lesions from periarteritis nodosa. They maintain that they are not different lesions but represent "varying responses to toxicity." They describe this evolution through the stages of granulation, hyalinization and fibrosis and eventually to scarring. Karsner and Bayless (27) in their study of the coronary arteries in rheumatic fever describe occasional lesions which may be interpreted as periarteritis nodosa. In 1923 Pappenheimer and von Glahn (28) reported rather characteristic findings in the larger vessels in rheumatic fever, previously observed by Klotz (29), characterized by dense scars in the vicinity of nutrient vessels both in the adventitia and in the media, often cellular. In two subsequent publications (30, 31) these observers described what seemed to be the earliest stage of these lesions. They found exudation of fibrin in and about the vessels, destructive changes in the cellular components of the vessel wall and around the vessel. These changes affected the vasa vasorum and many arterioles. They also noted the striking resemblance of these lesions to periarteritis nodosa. However, they differed from this lesion because of the absence of thrombosis and aneurysm formation, by the fact that the lesions affect vessels of lesser calibre and by the lesser degree of eosinophilic infiltration. Whether these represent entirely different reactions or are related, future studies must decide.

That the lesions of rheumatic fever may be due to hypersensitive reactions to bacterial products has been discussed repeatedly. One of the strongest advocates is Swift (32) who specially implicates the streptococcus, but the evidence has been only indirect, inasmuch as all attempts to reproduce the disease experimentally have been inconclusive.

In 1929, Gross, Loewe and Eliasoph (33) critically reviewed all previous experimental investigations to produce rheumatic fever and found none convincing.

They attempted to reproduce the lesions and especially the Aschoff body by various methods and failed. Among the many recent attempts the most promising have been those of Vaubel (34) and Rich and Gregory (35). By repeated intravenous injections of large doses of horse serum into rabbits in steadily increasing doses, Vaubel and Rich and Gregory not only obtained typical lesions of periarteritis nodosa but also endocardial thickenings and what appear to be typical Aschoff bodies. Very recently (1943) Rich and Gregory have produced lesions in rabbits by sensitization with foreign sera that resemble human rheumatic lesions closely, including Aschoff bodies; they ascribe varying susceptibility to explain why certain rabbits develop lesions of periarteritis nodosa and others lesions of rheumatic fever. While Rich and Gregory do not claim to have settled the problem of the etiology of rheumatic fever, their findings are certainly provocative.

b. Glomerulonephritis and periarteritis nodosa. The coexistence of anatomical glomerulonephritis and periarteritis nodosa has been reported repeatedly (36, 37, 29, 38, 39, 12, 40). The probability is strong that when they do occur together they are simultaneous reactions.

The association of periarteritis nodosa with glomerulonephritis, as with rheumatic fever, is significant in the light of recent experimental investigations concerning the pathogenesis of glomerulonephritis. All attempts to produce the lesion of glomerulonephritis, identical to that in man, have hitherto been largely unconvincing. Masugi (41) in 1933 produced what appear to be typical lesions by nephrotoxins derived by anaphylaxis. Later he and Osibasi (21) reported identical lesions obtained by injecting bacterial antigens derived from the bacillus coli, streptococcus and the staphylococcus. Similar results with a wide variety of antigens have been reported by Rich and Gregory (35), Smadel (42), Smadel and Farr (43), Hemprich (44), Weiss (45) and Ehrich, Wolf and Bartol (46). As a matter of fact, priority for the discovery of this mechanism must be given to Longcope (47) who as far back as 1913 produced lesions very comparable to those in man by repeated injections of horse serum and egg white in dogs, cats, guinea pigs and rabbits. Clinical progression of experimental glomerulonephritis induced by a nephrotoxin with fatal issue has been shown to occur in rats by Smadel and Farr (43) and in rabbits by Hemprich (44).

Significant are the reports of Masugi and his coworkers (21, 48). Masugi and Sato produced both glomerulonephritis and periarteritis nodosa in animals sensitized to egg white by injecting the antigen both into the general circulation and directly into the renal vein. In the first series generalized periarteritic lesions were found. In the second, the most marked lesions were found in the renal vessels. Masugi and Isabasi (21) produced coexisting lesions of glomerulonephritis and periarteritis nodosa in three of eight rabbits sensitized with living and dead staphylococcus albus. Miura (49) likewise induced both lesions simultaneously by sensitization with foreign serum.

This association is significant because a necrotizing arteritis, particularly common in the afferent artery of the glomerulus resembling that of periarteritis nodosa was noted in 10-20 per cent of autopsies in subacute and chronic glo-

merulonephritis (38). These lesions however differ from those of periarteritis nodosa by the absence of aneurysm formation, perivascular infiltration and their localization to the afferent arterioles. The significance and genesis of this lesion will be discussed later.

The evidence therefore submitted is, to say the least, strongly indicative that anaphylaxis is an important agent in the development of glomerulonephritis. It accords with the clinical observation, that glomerulonephritis does not arise during the height of the infection, but after it has subsided.

*Relation of periarteritis nodosa to hypertension.* Hypertension is a common accompaniment of periarteritis nodosa. In 11 of the 17 cases of Spiegel (12) in whom the blood pressure was reported, it was elevated in 8; in most, appreciably so. Of the 101 cases collected by Harris, Lynch and O'Hare (10) 64 had hypertension. That in many instances, the lesion was primary and the hypertension secondary is evidenced in the progressive rise under observation. Most likely the hypertension is of the Goldblatt type due to progressive ischemia. In acute glomerulonephritis both the nephritis and the hypertension are evidently simultaneous reactions. In the chronic phase an increase in blood pressure may be superimposed by progression of the periarteritic lesion. Either with or without glomerulonephritis, the clinical syndrome of "malignant hypertension" may be induced. However, in the clinical syndrome known clinically as the "malignant phase of essential hypertension" (Fishberg) and anatomically, nephrosclerosis, the relationship to periarteritis nodosa is by no means clear. The association of the malignant phase of essential hypertension with periarteritis nodosa has been reported frequently (1, 50, 51, 11, 52). It is probable that in some of the reported cases the clinical picture of "malignant hypertension" was established before the sequence of these two lesions could be established, but on the other hand the clinical histories of many patients reveal that the essential hypertension upon which the malignant phase was superimposed long antedated the onset of the periarteritis nodosa. In this sense, the periarteritis must be a secondary phenomenon. This is particularly disturbing if one regards periarteritis nodosa as invariably the result of an anaphylactic mechanism. There is no evidence whatever in the histories of these patients of any disorder that indicates an allergic mechanism. Three possibilities arise, first, that either some other mechanism is at fault; second, that the lesion is not a true periarteritis nodosa but one that closely simulates it; third, that the characteristic lesions of periarteritis may represent a later phase of a pre-existing lesion. There are cogent reasons for believing that the last assumption is correct, and that the lesion supposedly pathognomonic of "malignant hypertension," namely arteriolonecrosis, represents the primary phase of periarteritis nodosa. We shall not discuss the nosological status of malignant hypertension and its counterpart in morbid anatomy, malignant sclerosis, except to say that it is not a disease in the sense that it has a consistent etiology, clinical course and anatomical background, but is a syndrome and more particularly a phase with a number of antecedent clinical and morphological backgrounds. In any event, the consistent lesion found in malignant hypertension is arte-



riolonecrosis, most commonly found in the afferent arterioles of the glomeruli and to a lesser degree in other viscera. Usually these foci of necrosis are accompanied by an accelerated and intense arteriosclerosis. The one consistent clinical association is a high diastolic pressure and the issue now veers to a study of the relation between high diastolic pressure and arteriolonecrosis.

Some light has been thrown by the recent experiments of Wilson and Pickering (53) and Goldblatt (54) who found arteriolonecrosis in animals subject to prolonged and high intravascular pressure by the Goldblatt method with unilateral nephrectomy. (Neither of these observers measured the diastolic pressure.) Both these observers found the lesions widespread. Wilson and Pickering found a correlation in incidence between the height of the pressure and the lesion, but not necessarily to the duration of the hypertension. Goldblatt found that both excessive pressure and renal insufficiency were necessary factors in their production. Neither observer found these lesions in the kidney, which is not surprising in view of the low blood pressure in the renal artery proximal to the clamp. Subsequently, Wilson and Byrom (55) by producing high and sustained pressures in rats by narrowing of the renal vessel obtained necrosis of arterioles of the opposite kidney. As corroborative evidence, we cite the observations of Parker and Weiss (56) who found occasional arteriolonecrosis in the pulmonary circulation in some instances of tight mitral stenosis in which an extreme grade of hypertension of the pulmonary circulation was obvious.

The arteriolar necrotic lesions in human malignant hypertension resemble those found in periarteritis nodosa both in morphology and in size of the vessels affected and in distribution, although as a rule they are not nearly so ubiquitous. The distinguishing feature is the absence of the characteristic perivascular infiltration. Nevertheless many observers report transitions from none to perivascular infiltrations so pronounced that they invariably describe them as "resembling closely periarteritis nodosa" (57, 58, 38, 59, 60, 61, 62). Such infiltrations are found without glomerulonephritis and with glomerulonephritis (59). Horn, Klemperer, and Otani report such perivascular infiltrations as infrequent and that they occurred in areas where inflammatory lesions were more prominent. Shapiro (62) actually describes "transitions from moderately extensive necroses and slight periarteriolar infiltration to more extensive necrosis and a well defined picture of periarteritis nodosa as a later stage of extensive necrosis."

The point may be raised that these were instances of "primary" periarteritis nodosa with secondary "malignant hypertension", but this is hardly valid because the periarteritic lesions were found only occasionally as compared to the far greater number of necrotic lesions; in "primary" periarteritis nodosa, the lesions are widespread.

That the arteriolonecrosis of "malignant" hypertension and periarteritis nodosa are genetically akin receives some corroboration from experimental observations in which excessive and prolonged hypertension are produced. Wilson and Pickering (53) using the Goldblatt technique showed illustrations of lesions indistinguishable from those of periarteritis nodosa. Cromartie (63),



by the Goldblatt technique produced typical lesions in rats between 6 and 12 months old. These were never normally present in rats less than 500 days old. Selye and Pavitz (64) also obtained typical periarteritic lesions in rats using desoxycorticosterone acetate combined with unilateral nephrectomy to produce excessive hypertension. The kidney showed the changes usually found in malignant nephrosclerosis. Goldblatt (54) in his earliest report on the vascular changes following the production of sustained and high intravascular pressure values found perivascular infiltration with polymorphonuclear leucocytes and lymphocytes in one case, but he ascribed these lesions as the result of a "probable coincidental infection." The precise mechanism whereby arteriolonecrosis is produced in both clinical and experimental malignant hypertension is not entirely clear. Although in experimental animals, renal insufficiency in addition to high intravascular pressures is an essential part of the mechanism, according to Goldblatt (54) clinically, periarteritis nodosa is by no means uncommon in the absence of renal insufficiency (38). Does the high diastolic pressure interfere with the nutrition of the vessel wall, or is a substance produced that acts as a necrotizing agent? (65). It is reasonable to assume that the perivascular infiltration with polymorphonuclears arise by chemotaxis. Most necrotic foci, whether intra- or extravascular, or whether they are infectious in origin or not, eventually become surrounded by such infiltrations. In the later stages the perivascular infiltration becomes granulomatous, histiocytes are predominant, and eventually fibrosis with its sequelae ensue. This as we have pointed out are precisely the sequence of events that occurs in classical instances of periarteritis nodosa. This mechanism would also account for the occasional occurrence of the lesions resembling periarteritis nodosa in other vascular lesions that are attended by necrosis, for instance in lupus erythematosus (66) and in the type of non-bacterial thrombotic endocarditis associated with fever, arthritis and serositis reported by Friedberg, Gross and Wallach (67). In other words, there is sufficient evidence that leads us to believe that the primary lesion is the necrosis, and the perivascular lesion is secondary. The relationship between arteriolonecrosis and periarteritis nodosa is essentially a quantitative rather than a qualitative one. Why the perivascular inflammatory reaction varies so in intensity depends, in all probability, upon the nature and intensity of the primary insult and the varying tissue reactivity of the individual's tissues. The morphological variations encountered depend upon the phase of its biological progression, and to a large extent the clinical expression is modified by the same token.

When one removes the three most common backgrounds of periarteritis nodosa, namely glomerulonephritis, rheumatic fever and the syndrome of "malignant" hypertension, only a small moiety remains in which the periarteritis is the sole incriminating lesion. Even in this fraction, periarteritis is a secondary event or a complication, and bears the same relation to the basic disease as, for instance, pleuritis to pneumonia. Nevertheless it deserves clinical recognition, in order to study methods to counteract or neutralize the primary mechanism. The possibility of healing rests on its recognition in its early stages.

*Clinical aspects.* The clinical aspects of periarteritis nodosa are the resultant of three large clinical backgrounds, rheumatic fever, glomerulonephritis and "malignant" hypertension plus the consequences of the widespread lesions, affecting the circulation and function of many organs. Periarteritis nodosa therefore gives rise to a host of clinical expressions, depending on the degree and extent of functional impairment. For this reason, various "types" have been formulated, the cardiac, renal, gastro-intestinal, pulmonary, central nervous systemic, cutaneous, polyserositic, etc. (12). It is obvious that there is nearly always an overlapping, so that these types are usually combined. Why one organ is more involved than another is entirely speculative. It is not surprising therefore that the antemortem diagnosis of periarteritis nodosa is only infrequently made. In our experience, the more important diagnostic criteria depend on; first, an awareness of the possibility of such a diagnosis, second, the recognition of the multiple visceral involvement, especially with bizarre combinations, such as peripheral neuritis or fever, and third, evidences of predominant vascular disease, such as hypertension and hemorrhages into or from various viscera especially the kidney, intestine, skin and retina.

#### BIBLIOGRAPHY

1. KLEMPERER: Arch. Path., 13: 354, 1932.
2. FISHBERG: Virchows Arch. f. path. Anat., 140: 483, 1923.
3. GROSS, KUGEL AND EPSTEIN: Am. J. Path., 11: 253, 1935.
4. ARKIN: Am. J. Path., 6: 401, 1930.
5. BAEHR AND MANGES: Am. J. M. Sc., 172: 162, 1921.
6. KEEGAN: Arch. Int. Med., 36: 189, 1925.
7. JAGER: Virchows Arch. f. path. Anat., 227: 1, 1920.
8. SPIRO: Virchows Arch. f. path. Anat., 227: 1, 1920.
9. CARLING AND BRAXTON HICKS: Lancet, 1: 1001, 1923.
10. HARRIS, LYNCH AND O'HARE: Arch. Int. Med., 63: 1163, 1939.
11. GRANT: Clin. Sc., 4: 245, 1940.
12. SPIEGEL: Arch. Int. Med., 63: 993, 1936.
13. PLAUT: Arch. Path., 13: 355, 1932.
14. FRIEDBERG AND GROSS: Arch. Int. Med., 54: 170, 1934.
15. JOEST AND HARZER: Ziegler's Beitr., 69: 85, 1921.
16. GRUBER: Virchows Arch. f. path. Anat., 258: 441, 1925.
17. COHEN, KLINE AND YOUNG: J. A. M. A., 107: 1555, 1936.
18. RACKEMANN AND GREENE: Tr. A. Am. Physicians, 54: 112, 1939.
19. METZ: Ziegler's Beitr., 88: 17, 1931-32.
20. GERBER: Arch. Path., 21: 776, 1936.
21. MASUGI AND OSIBASI: Ziegler's Beitr., 96: 391, 1935-36.
22. CLARK AND KAPLAN: Arch. Path., 24: 458, 1937.
23. RICH: Bull. Johns Hopkins Hosp., 71: 123, 1942.
24. RICH AND GREGORY: Bull. Johns Hopkins Hosp., 72: 65, 1943.
25. GERLACH: Virchows Arch. f. path. Anat., 297: 294, 1923.
26. KLINGE AND VAUBEL: Virchows Arch. f. path. Anat., 281: 701, 1931.
27. KARSNER AND BAYLESS: Am. Heart J., 9: 557, 1933-34.
28. PAPPENHEIMER AND VON GLAHN: J. Med. Research., 44: 489, 1923-24.
29. KLOTZ: J. Med. Research, 47: 1, 1917-18.
30. VON GLAHN AND PAPPENHEIMER: Am. J. Path., 2: 151, 1926.
31. VON GLAHN AND PAPPENHEIMER: Am. J. Path., 2: 235, 1926.
32. SWIFT: J. A. M. A., 92: 2071, 1929.

33. GROSS, LOEWE AND ELIASOPH: J. Exper. Med., 50: 41, 1929.
34. VAUBEL: Zeigler's Beitr., 89: 374, 1932.
35. RICH AND GREGORY: Bull. Johns Hopkins Hosp., 73: 235, 1943.
36. BAEHR: Tr. A. Amer. Physicians, 46: 87, 1931.
37. LAMB: Arch. Int. Med., 14: 481, 1914.
38. KLEMPERER AND OTANI: Arch. Path., 11: 60, 1931.
39. JACOBSEN: Arch. Path., 16: 595, 1933.
40. HALPEREN AND TRUBECK: Arch. Path., 15: 35, 1933.
41. MASUGI: Ziegler's Beitr., 91: 82, 1933.
42. SMADEL: J. Exper. Med., 64: 921, 1937.
43. SMADEL AND FARR: J. Exper. Med., 65: 527, 1937.
44. HEMPRICH: Ztschr. f. d. ges. exper. Med., 95: 308, 1935.
45. WEISS: Zeigler's Beitr., 92: III, 1935-36.
46. EHRLICH, WOLF AND BARTOL: J. Exper. Med., 67: 769, 1938.
47. LONGCOPE: J. Exper. Med., 18: 678, 1913.
48. MASUGI AND SATO: Virchows Arch. f. path. Anat., 293: 615, 1934.
49. MIURA: Tr. Soc. path. Jap., 30: 778, 1940.
50. GOLDBLOOM AND LIEBERSON: Am. J. Med. Sc., 198: 52, 1939.
51. BAU: Deutsche med. Wchnschr., 60: 1158, 1934.
52. DEROW AND ALTSCHULE: Ann. Int. Med., 14: 1738, 1941.
53. WILSON AND PICKERING: Clin. Sc., 3: 343, 1937-38.
54. GOLDBLATT: J. Exper. Med., 67: 809, 1938.
55. WILSON AND BYROM: Lancet, 236: 136, 1939.
56. PARKER AND WEISS: Am. J. Path., 12: 573, 1936.
57. MURPHY AND GRILL: Arch. Int. Med., 46: 75, 1930.
58. HÜCKEL: Virchows Arch. f. path. Anat., 246: 447, 1930.
59. HORN, KLEMPERER AND STEINBERG: Arch. Int. Med., 70: 260, 1942.
60. SCHURMAN AND MACMAHON: Virchows Arch. f. path. Anat., 291: 47, 1933.
61. STERNBERG: Arch. Int. Med., 44: 272, 1929.
62. SHAPIRO: Arch. Int. Med., 48: 199, 193.
63. CROMARTIE: Am. J. Med. Sc., 206: 66, 1943.
64. SELYE AND PENTZ: Canad. M. A. J., 49: 264, 1943.
65. WINTERNITZ: In Blood, heart and circulation, Am. A. Advancement Sc., 114: 1940.
66. KLEMPERER, POLLACK AND BAEHR: Arch. Path., 32: 569, 1941.
67. FRIEDBERG, GROSS AND WALLACH: Arch. Int. Med., 58: 662, 1936.
68. KLEMPERER: Personal communication.

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*The Postcholecystectomy Syndrome and its Treatment.* R. COLP. Bull. New York Acad. Med., 20: 4, 203, April, 1944.

The removal of the gall bladder is frequently followed by acute symptoms identical to those which existed prior to operation. This symptom complex is called the postcholecystectomy syndrome and may resemble cholecystitis and cholelithiasis in all their various clinical manifestations. The syndrome is most frequent in cases characterized by definite colic pre-operatively and in which functional disturbances were demonstrated by cholecystography, but in which surgical exploration revealed the absence of gall bladder lesions or the presence of a noncalculous cholecystitis. It seemed less frequent in cases of calculous cholecystitis. The etiology of the postcholecystectomy syndrome may usually be attributed to a dyskinesia of the sphincter mechanism. This sphincter spasm may be stimulated either by local causes or by intrabiliary factors such as recurrent or residual calculosis of the cystic or common bile duct, partial traumatic strictures of the choledochus, cholangitis or pancreatitis. The dyssynergia may be initiated by psychic disturbances, glandular dyscrasias or as the result of a spastic colon. Dyskinesia of the ampullary sphincter after cholecystectomy may play a significant rôle in the postcholecystectomy syndrome. A pancreatic reflux as a result of spasm may cause acute pancreatitis or chronic choledochitis. Medical treatment should always be tried before advising surgery. Small hypodermic doses of morphine used as a therapeutic test may be used to substantiate a diagnosis of dyskinesia. The author has successfully divided spastic sphincters of the common bile duct and ampulla in 7 cases with good clinical results by means of a specially designed instrument which was introduced through the common bile duct.

*Advances in Endocrine Therapy.* R. T. FRANK. Am. J. Obst. & Gynec., 47: 4, 561, April, 1944.

The historical background, discovery and classification of the hormones fall into three main groups—the simple amino acids or amines, including thyroxin and epinephrine; the "protein" hormones among which are the pituitary extracts, insulin and parathyroid extracts; and the steroid hormones which embrace both male and female sex hormones, as well as the adrenal hormones. In addition synthetic products which may or may not resemble chemically the hormones having similar action have been elaborated. The exact indication for the use of the various hormones is given as well as our present knowledge permits. Emphasis is placed on the importance of diagnosis, selection of therapy, and limitations of the same.

*Permanent metachromatic staining of gastric mucus smears.* M. HESS AND F. HOLLANDER. J. Lab. & Clin. Med., 29: 321, March, 1944; correction of typographical error, *ibid.*, 29: 449, April, 1944.

The chief difficulty encountered in the use of toluidine blue and similar metachromatic dyes for the staining of mucin and related substances arises from the transience of their bi-chromatic effect. The red metachromatic staining of mucin always changes to the blue normochromatic appearance as the section undergoes dehydration. The present paper reports a new technique for the staining of mucus smears with toluidine blue, as a result of which metachromatic differentiation of intra- and extra-cellular mucin from nuclei and cytoplasm is permanent. Such smears have retained their metachromasia for 2 years or more. The method has been applied to mucus of the cervix uteri with equal success.

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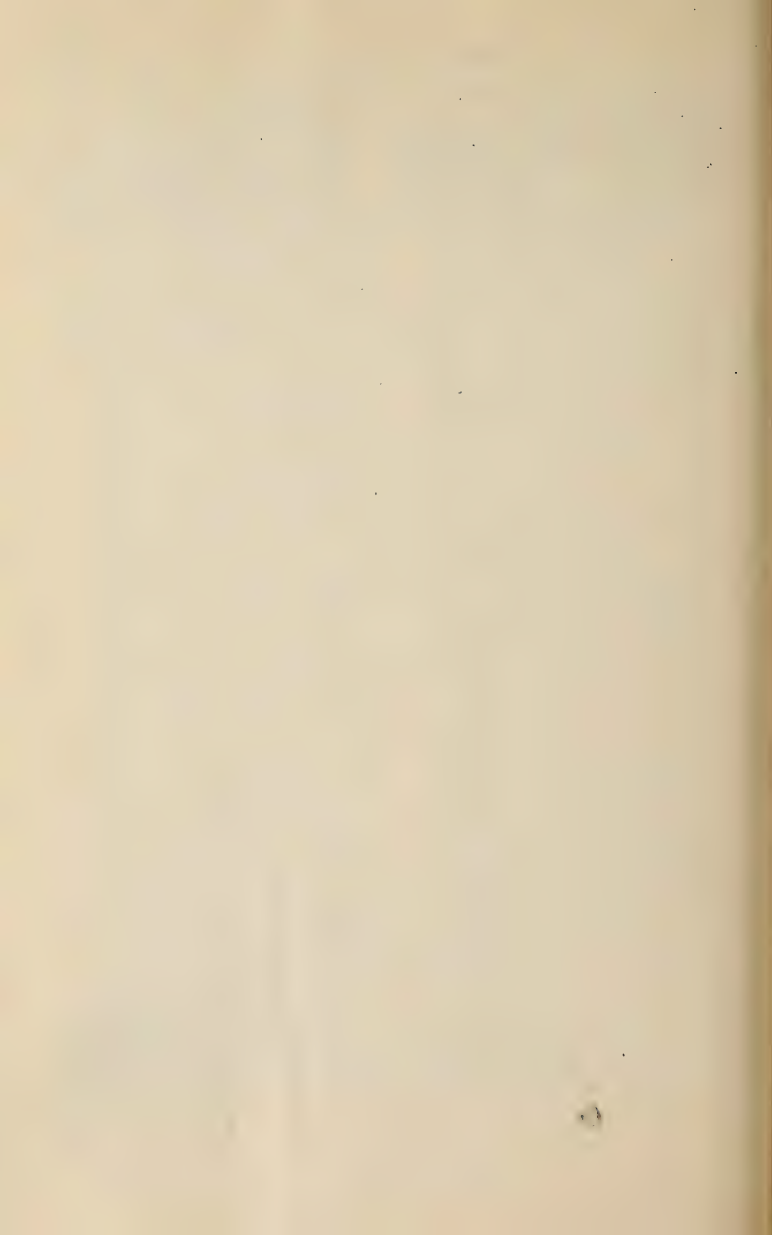
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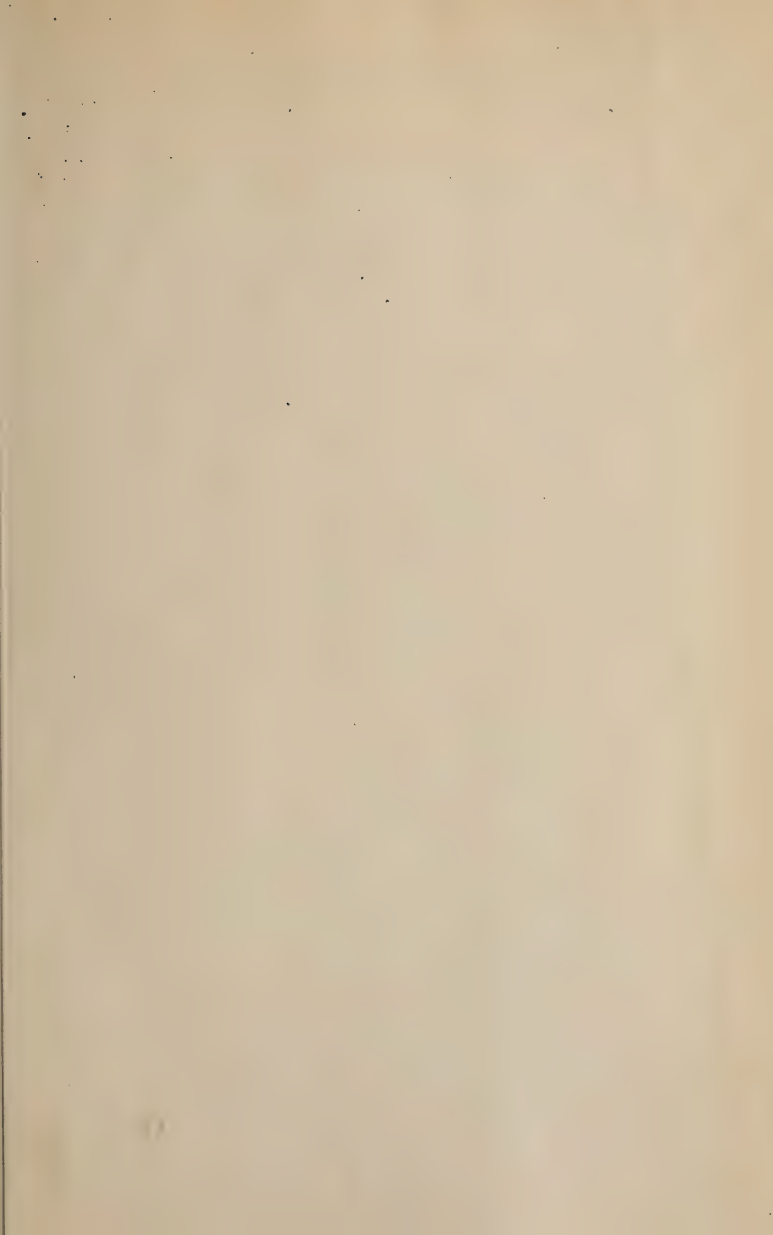


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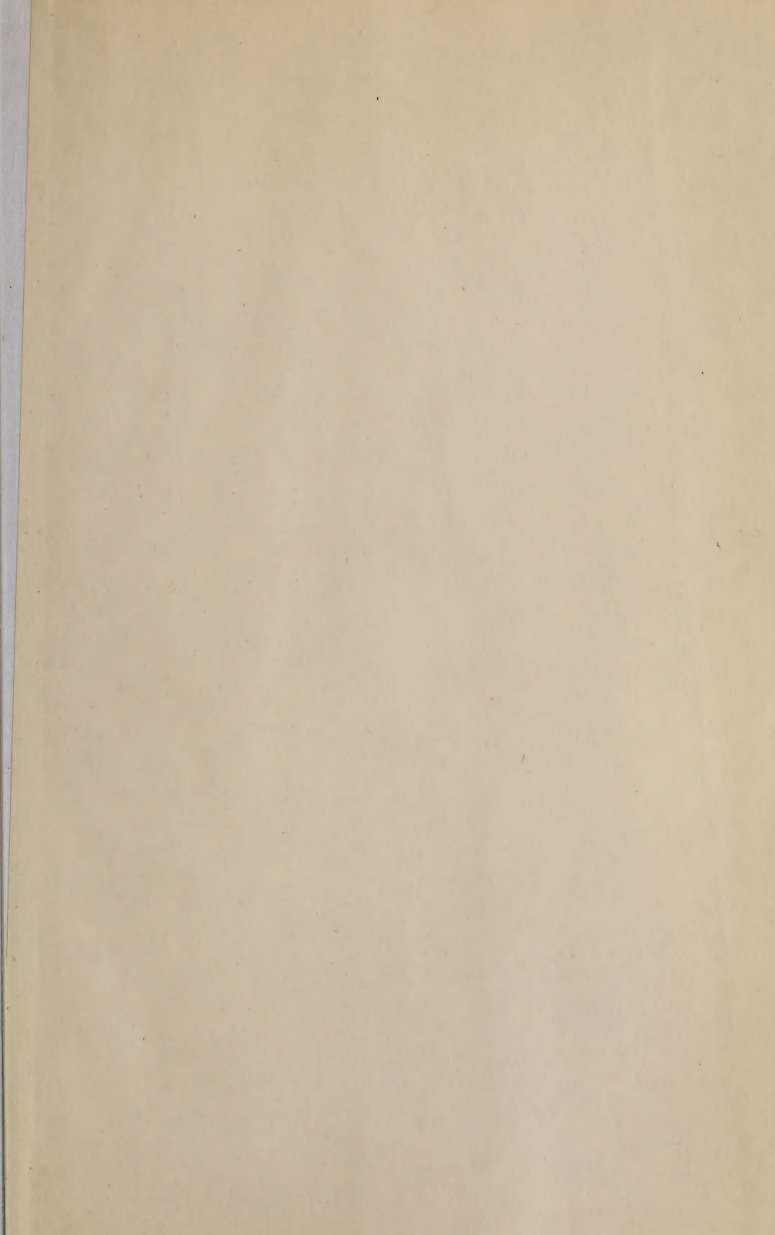


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- Z**AZEELA, H. A., and Weinroth, L. A., Thrombo-angiitis obliterans and diabetes mellitus in the same patient, \*776
- Zeman, F. D., Life's Later Years, \*783, 833, 890, 939

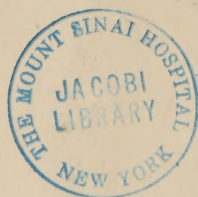












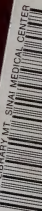
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